

FILE 'REGISTRY' ENTERED AT 16:06:38 ON 12 FEB 2003

L1 STRUCTURE UPLOADED
L2 0 S L1 FUL
L3 STRUCTURE UPLOADED
L4 0 S L3 FUL
L5 STRUCTURE UPLOADED
L6 91 S L5 FUL
L7 88 S L6 AND CAPLUS/LC
L8 3 S L6 NOT L7
L9 STRUCTURE UPLOADED
L10 0 S L9 FUL

FILE 'CAPLUS' ENTERED AT 16:10:17 ON 12 FEB 2003

=> s 16

L11 62 L6

=> d 1-62 ibib abs hitstr

L11 ANSWER 1 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:526269 CAPLUS

DOCUMENT NUMBER: 137:292513

TITLE: Effects of hyperglycemia on oxygenation,
radiosensitivity and bioenergetic status of
subcutaneous RIF-1 tumors

AUTHOR(S): Nadal-Desbarats, L.; Poptani, H.; Oprysko, P.;
Jenkins, W. T.; Busch, T. M.; Nelson, D. S.;

Glickson,

J. D.; Koch, C. J.; Evans, S. M.
CORPORATE SOURCE: Department of Radiology, University of Pennsylvania,
Philadelphia, PA, 19104, USA

SOURCE: International Journal of Oncology (2002), 21(1),
103-110

CODEN: IJONES; ISSN: 1019-6439

PUBLISHER: International Journal of Oncology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Since tissue O tension is a balance between delivery and consumption of
O,

considerable effort was directed at increasing the former and/or
decreasing the latter. Techniques to decrease the rate of cellular O
consumption (increasing the distance O can diffuse into tissues) include
increasing glycolysis by administering supraphysiol. levels of glucose.
We have examd. the effect of hyperglycemia produced by i.v. glucose
infusion on the tissue oxygenation and radiation response of s.c.
implanted murine radiation induced fibrosarcomas (RIF-1). A 0.3 M
glucose

soln. was delivered via tail vein injection according to a protocol that
maintained glucose at a plasma concn. of 17.+-1 mM. The effect of this
treatment on radiation response (clonogenic and growth delay studies),
tumor oxygenation (needle electrode pO2 and

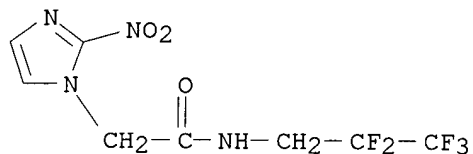
2-[2-nitro-1H-imidazol-1-yl]-N-

(2,2,3,3,3-pentafluoropropyl) acetamide (EF5) binding), and tumor
bioenergetics and pH (31P NMR spectroscopy) was examd. Systemic
measurements included hematocrit and blood glucose and lactate concns.

The results of these studies suggest that these s.c. implanted RIF-1
tumors are both radiobiol. and metabolically hypoxic and that i.v.

glucose

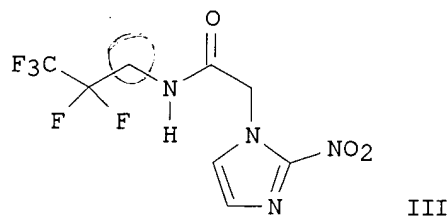
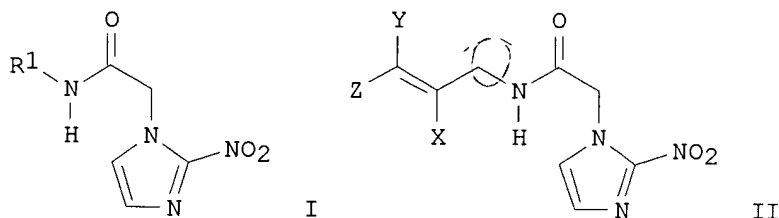
infusion is not an effective method of modifying this metabolic state.
IT **152721-37-4**, EF5
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(hyperglycemia effect on oxygenation, radiosensitivity, and EF5
binding
in s.c. RIF-1 tumors)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
(CA INDEX NAME)

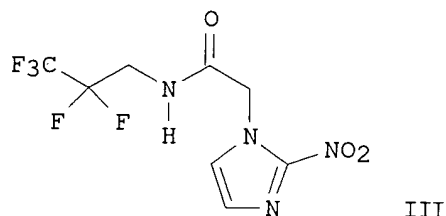
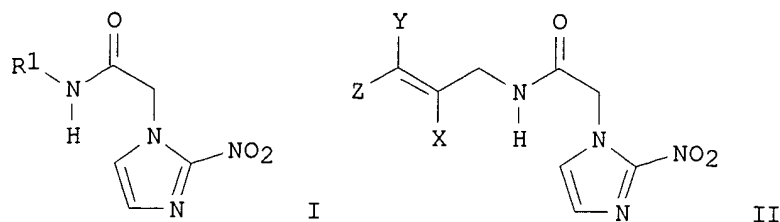


L11 ANSWER 14 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 2001:78365 CAPLUS
 DOCUMENT NUMBER: 134:147601
 TITLE: Preparation of fluorinated nitroimidazole compounds
 and their labeled counterparts for the detection of
 hypoxia
 INVENTOR(S): Dolbier, William R.; Li, An-Rong; Koch, Cameron J.;
 Kachur, Alexander V.
 PATENT ASSIGNEE(S): The Trustees of the University of Pennsylvania, USA
 SOURCE: PCT Int. Appl., 33 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007414	A1	20010201	WO 2000-US40437	20000720
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG EP 1202973 A1 20020508 EP 2000-960168 20000720 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL PRIORITY APPLN. INFO.: US 1999-144747P P 19990721 WO 2000-US40437 W 20000720				

GI





AB Methods for prepg. novel fluorinated nitroimidazoles I [R1 = CH2CHFCH2F, CH2CHFCHF2, CH2CHF3, CH2CH2CH2F, CH2CF2CHF2, and CH2CF2CF3], their 18F-labeled counterparts [at least one F is 18F], along with their corresponding intermediates II [X, Y, and Z are independently H or F] are disclosed. Thus, III (EF5) was prepd. by fluorination of the allyl precursor 2-(2-nitro-1H-imidazol-1-yl)-N-(2,3,3-trifluoroallyl)acetamide (II; X = Y = Z = F). The title compds. are disclosed as agents for non-invasive imaging techniques, such as PET, for detecting tissue hypoxia

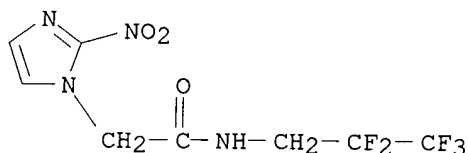
and demonstrated in PET imaging of a tumor-bearing rat treated with [18F]-labeled EF5. Diagnostic kits useful in practicing the methods of claimed invention are also provided.

IT **152721-37-4P 322637-51-4P 322637-52-5P**
322637-53-6P 322637-54-7P 322637-55-8P
322637-56-9P

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (prepn. of fluorinated nitroimidazoles and their labeled counterparts as medical imaging agents for the detection of hypoxia)

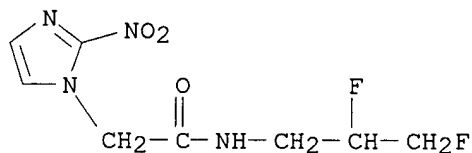
RN 152721-37-4 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
 (CA INDEX NAME)



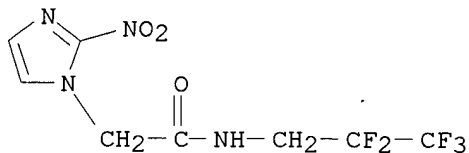
RN 322637-51-4 CAPLUS

CN 1H-Imidazole-1-acetamide, N-(2,3-difluoropropyl)-2-nitro-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



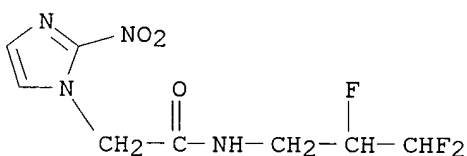
RN 322637-52-5 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



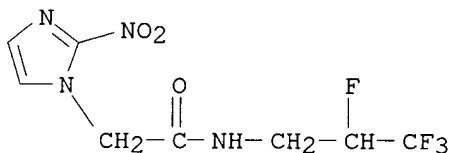
RN 322637-53-6 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,3,3-trifluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



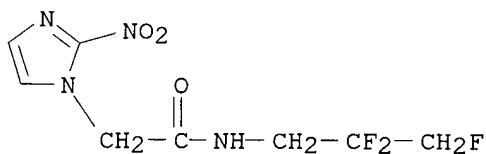
RN 322637-54-7 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,3,3,3-tetrafluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



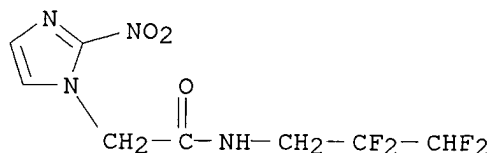
RN 322637-55-8 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3-trifluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



RN 322637-56-9 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3-tetrafluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L11 ANSWER 15 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:806871 CAPLUS

DOCUMENT NUMBER: 134:207753

TITLE: [18F]-EF5, a marker for PET detection of hypoxia:
synthesis of precursor and a new fluorination
procedure

AUTHOR(S): Dolbier, W. R.; Li, A.-R.; Koch, C. J.; Shiu, C.-Y.;
Kachur, A. V.

CORPORATE SOURCE: Department of Chemistry, University of Florida,
Gainesville, FL, 32611, USA

SOURCE: Applied Radiation and Isotopes (2000), Volume Date
2001, 54(1), 73-80

CODEN: ARISEF; ISSN: 0969-8043

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 134:207753

AB There is a great deal of clin. and exptl. interest in detg. tissue
hypoxia

using non-invasive imaging methods. The authors have previously
developed

EF5, 2-(2-nitro-1[H]-imidazol-1-yl)-N-(2,2,3,3,3-
pentafluoropropyl)acetamide, with both invasive and non-invasive hypoxia
detection in mind. EF5 and other 2-nitroimidazoles are used to detect
hypoxia, because the rate of their bio-reductive metab. is inversely
dependent on oxygen partial pressure. Such metab. leads to the formation
of covalent adducts within the metabolizing cells. Previously, the
authors have described the invasive detection of these adducts by highly
specific monoclonal antibodies after tissue biopsy. In this work, the
authors synthesized 18F-labeled EF5,

[18F]-2-(2-nitro-1[H]-imidazol-1-yl)-

N-(2,2,3,3,3-pentafluoropropyl)acetamide, in greater than 10% yield by
direct fluorination of the newly synthesized precursor

2-(2-nitro-1[H]-imidazol-1-yl)-N-(2,3,3-trifluoroallyl)acetamide by
[18F]-F₂ in trifluoroacetic acid. The objective was to optimize the
electrophilic fluorination of the fluorinated alkene bond with fluorine
gas, a new method of 18F-labeling of polyfluorinated mols. Previous
biodistribution studies in mice have demonstrated uniform access of EF5

to

all tissues with bioelimination dominated by renal excretion. When
[18F]-EF5 was injected into a rat followed by urine collection and anal.,
the authors found no detectable metab. to other radioactive compds.

Thus,

[18F]-EF5 should be well suited for use as a non-invasive hypoxia marker with detection using positron emission tomog. (PET).

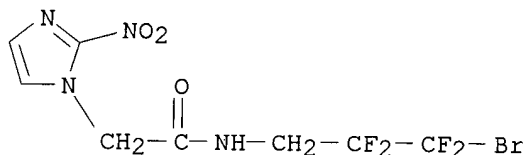
IT **328386-75-0P**

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(using electrophilic fluorination in acidic medium to prep. [18F]-EF5, marker for PET detection of hypoxia)

RN 328386-75-0 CAPLUS

CN 1H-Imidazole-1-acetamide, N-(3-bromo-2,2,3,3-tetrafluoropropyl)-2-nitro- (9CI) (CA INDEX NAME)



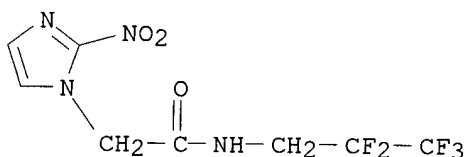
IT **152721-37-4P, EF5**

RL: SPN (Synthetic preparation); PREP (Preparation)

(using electrophilic fluorination in acidic medium to prep. [18F]-EF5, marker for PET detection of hypoxia)

RN 152721-37-4 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)



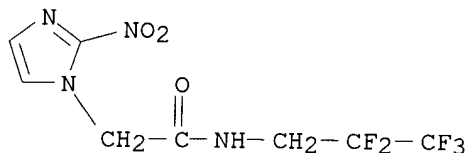
IT **322637-52-5P**

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(using electrophilic fluorination in acidic medium to prep. [18F]-EF5, marker for PET detection of hypoxia)

RN 322637-52-5 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)

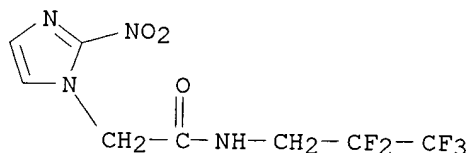


REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS

FORMAT

RECORD. ALL CITATIONS AVAILABLE IN THE RE

ACCESSION NUMBER: 2000:248505 CAPLUS
 DOCUMENT NUMBER: 133:29066
 TITLE: Detection of hypoxia in human squamous cell carcinoma by EF5 binding
 AUTHOR(S): Evans, Sydney M.; Hahn, Stephen; Pook, Deirdre R.; Jenkins, W. Timothy; Chalian, Ara A.; Zhang, Paul; Stevens, Craig; Weber, Randall; Weinstein, Gregory; Benjamin, Ivor; Mirza, Natasha; Morgan, Mark; Rubin, Steven; McKenna, W. Gillies; Lord, Edith M.; Koch, Cameron J.
 CORPORATE SOURCE: Schools of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA
 SOURCE: Cancer Research (2000), 60(7), 2018-2024
 CODEN: CNREA8; ISSN: 0008-5472
 PUBLISHER: American Association for Cancer Research
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Localization and quantitation of 2-nitroimidazole drug binding in low pO₂ tumors is a technique that can allow the assessment of hypoxia as a predictive assay. EF5 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl) acetamide] is such a drug, and it has been shown to be predictive of radiation response in rodent tumors. Using fluorescence immunohistochem. techniques, data on the presence, distribution, and levels of EF5 binding as a surrogate for hypoxia in human head and neck and uterine cervix squamous-cell cancers (SCCs) are provided. Six patients with SCC were studied. Four patients had head and neck tumors, and two had uterine cervix cancers. The incubation of fresh tissue cubes in EF5 under hypoxic conditions ("ref. binding") demonstrated that all tumors were capable of binding drug, and that this binding varied by a factor of 2.9-fold (174.5-516.1) on an abs. fluorescence scale. In the five patients treated at the lowest drug doses (9 mg/kg), in situ binding was quantifiable. For all six patients, the max. rate of in situ binding varied by a factor of 6.7 between the lowest and highest binding tumor (24.8-160.3) on an abs. fluorescence scale. In tumors with high binding regions, intratumoral heterogeneity was large, extending from minimal fluorescence (<1%) up to 88.6% of ref. binding. In tumors with minimal binding, there was little intratumoral heterogeneity. These studies demonstrate substantial heterogeneity of in situ binding between and within individual squamous-cell tumors.
 IT 152721-37-4, EF5
 RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
 (detection of hypoxia in human squamous-cell carcinoma by EF5 binding)
 RN 152721-37-4 CAPLUS
 CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
 (CA INDEX NAME)



L11 ANSWER 13 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:113367 CAPLUS

DOCUMENT NUMBER: 135:134082

TITLE: Hypoxia in human intraperitoneal and extremity sarcomas

AUTHOR(S): Evans, S. M.; Hahn, S. M.; Magarelli, D. P.; Zhang, P.

J.; Jenkins, W. T.; Fraker, D. L.; Hsi, R. A.; McKenna, W. G.; Koch, C. J.

CORPORATE SOURCE: From the School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA, USA

SOURCE: International Journal of Radiation Oncology, Biology, Physics (2001), 49(2), 587-596
CODEN: IOBPD3; ISSN: 0360-3016

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The presence of hypoxia, measured by needle electrodes, was shown to be assocd. with poor patient outcome in several human tumor types, including soft tissue sarcomas. The present report emphasizes the evaluation of hypoxia in soft tissue sarcomas based upon the binding of the 2-nitroimidazole drug EF5 (2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl) acetamide). EF5 has previously been shown to be predictive of radiation response in animal tumors and in in vitro studies.

The authors have also previously reported studies of EF5 binding in human squamous cell tumors. Using fluorescent immunohistochem. techniques, the authors provide data on the presence and distribution of EF5 binding, as

a surrogate for hypoxia, in human spindle cell tumors. Patients with spindle cell tumors who were scheduled for tumor surgery were asked to participate in the phase I trial of EF5. Approx. 48 h preoperatively,

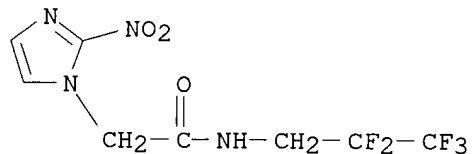
EF5 was administered i.v. at doses between 9 and 21 mg/kg. Binding in frozen sections of biopsied tissues was detd. using monoclonal antibodies

labeled with the green-excited, orange-emitting fluorescent dye, Cy3.

Calibration studies were performed in vitro by incubating fresh tumor tissue cubes obtained from each patient with EF3 (an analog of EF5) under hypoxic conditions ("ref. binding"). The goal of these calibration studies was

to quantify the maximal binding levels possible in individual patient's tissues. The relationship between binding (in situ based on EF5 binding) and ref. binding (in vitro based on EF3 binding) was detd. 8 Patients were studied; 3 of these patients had gastrointestinal stromal tumors (GIST). The incubation of tumor tissue cubes in EF3 under hypoxic conditions demonstrated that all tumors bound drug to a similar extent. Ref. binding showed a 3.2-fold variation in median fluorescence (113-356) on an abs. fluorescence scale, calibrated by a Cy3 dye std. In situ binding in the brightest tumor section varied by a factor of 25.4 between the lowest and highest binding tumor (7.5-190.2). Heterogeneity of highest binding was greater between tumors than within individual tumors. A correspondence between EF5 binding and Eppendorf needle electrode studies was seen in the 5 patients with non-GISTs. Inter- and intratumoral heterogeneity of EF5 binding in spindle cell tumors was documented. Patterns of binding consistent with diffusion limited hypoxia

are present in human spindle cell neoplasms.
 IT 152721-37-4, EF5
 RL: ARG (Analytical reagent use); BUU (Biological use, unclassified);
 ANST (Analytical study); BIOL (Biological study); USES (Uses)
 (hypoxia anal. in sarcomas by immunohistochem. using EF5)
 RN 152721-37-4 CAPLUS
 CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
 (CA INDEX NAME)



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR
 THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE
 FORMAT

L11 ANSWER 7 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:790212 CAPLUS

DOCUMENT NUMBER: 136:67942

TITLE: Hypoxia-inducible factor-1.alpha. is an intrinsic marker for hypoxia in cervical cancer xenografts

AUTHOR(S): Vukovic, Vojislav; Haugland, Hans Kristian; Nicklee, Trudey; Morrison, Andrew J.; Hedley, David W.

CORPORATE SOURCE: Departments of Medical Biophysics, Ontario Cancer Institute/Princess Margaret Hospital, Toronto, ON,

M5G

2M9, Can.

SOURCE: Cancer Research (2001), 61(20), 7394-7398

CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The hypoxia-inducible factor 1 (HIF-1) is known to induce the expression of several proteins linked to the maintenance of oxygen homeostasis, cellular energy metab., and tumor progression. Its .alpha. subunit (HIF-1.alpha.) is stabilized under hypoxic conditions and, therefore, might represent an intrinsic marker for tissue, hypoxia. Here we report on the spatial relationship between HIF-1.alpha. and the nitroimidazole hypoxia marker EF5 in cervical carcinoma xenografts, and on their spatial relationship to tumor blood vessels. EF5 was administered to mice bearing

ME180 and SiHa cervical cancer xenografts. Frozen tumor tissue sections, triple-stained for HIF-1.alpha., the endothelial cell marker CD31, and EF5, were imaged using wide-field multiparameter immunofluorescence microscopy. Expression levels of EF5 and HIF-1.alpha. were similar in ME180 xenografts, but the percentage of tumor area stained with EF5 was significantly smaller than the percentage of HIF-1.alpha.-pos. area in SiHa tumors. In both tumor types the EF5-HIF-1.alpha. overlap was statistically significant, thus confirming their spatial and temporal colocalization. Spatial distribution anal. of EF5 and HIF-1.alpha. is consistent with different pO2 value "thresholds" for EF5 binding and HIF-1.alpha. expression. Summarized, our results indicate that HIF-1.alpha. is a useful intrinsic marker for hypoxia in cervical carcinoma xenografts.

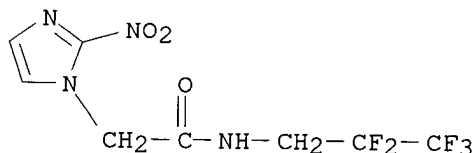
IT 152721-37-4

RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)

(hypoxia-inducible factor-1.alpha. as intrinsic marker for hypoxia in cervical carcinoma xenografts)

RN 152721-37-4 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L11 ANSWER 8 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:644457 CAPLUS

DOCUMENT NUMBER: 137:29877

TITLE: Pharmacokinetics of EF5

[2-(2-nitro-1-H-imidazol-1-yl)-

N-(2,2,3,3,3-pentafluoropropyl) acetamide] in human patients: implications for hypoxia measurements in vivo by 2-nitroimidazoles

AUTHOR(S): Koch, C. J.; Hahn, S. M.; Rockwell, K., Jr.; Covey, J.

M.; McKenna, W. G.; Evans, S. M.

CORPORATE SOURCE: University of Pennsylvania School of Medicine,

Radiation Oncology, Philadelphia, PA, 19104-6072, USA

SOURCE: Cancer Chemotherapy and Pharmacology (2001), 48(3), 177-187

CODEN: CCPHDZ; ISSN: 0344-5704

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Objectives: Pharmacokinetic studies were performed on the 1st 28 patients enrolled in a phase I trial to det. the ability of EF5

[2-(2-nitro-1-H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl) acetamide] to detect hypoxia in human tumors in the absence of patient toxicity.

Methods: EF5 was made in purified form and formulated for i.v. injection by the National Cancer Institute. After obtaining consent from the patients, EF5 was administered and blood samples were drawn at various times over approx. 48 h. For most patients it was possible to collect total urine at approx. 8-h intervals. EF5 in plasma and urine was analyzed by high-performance liq. chromatog. Results: EF5's blood plasma concn. followed a simple exponential decay following infusion. The

plasma

half-life was 11.7 h and was not affected by drug dose (9 to 28 mg/kg), fractional urine recovery, patient wt., or gender. Abs. plasma values suggested even biodistribution of the drug throughout the soft tissue

with

a vol. of distribution equal to 0.56 l/kg. Despite the relatively high lipid partition coeff. (logP=0.6), EF5 was excreted primarily (.ltoreq. 70%) via kidney clearance. No drug metabolites (e.g. retaining the 2-nitroimidazole chromophore) were detected in either plasma or urine.

No

toxicity was found at drug doses adequate to detect tumor hypoxia.

Conclusions: Currently held paradigms of 2-nitroimidazole metab. (e.g. clearance rate and toxicity as affected by octanol/water partition

coeff.)

are discussed. The results reported herein suggest that EF5 is biol. stable with predictable pharmacokinetics. EF5's consistent half-life and clearance properties will allow quant. anal. of EF5 binding relative to tissue oxygen levels.

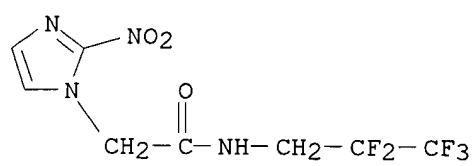
IT 152721-37-4, EF5

RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(pharmacokinetics of EF5 in human cancer patients)

RN 152721-37-4 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)



L11 ANSWER 32 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1996:494670 CAPLUS
 DOCUMENT NUMBER: 125:162343
 TITLE: Detection of hypoxia with reagents containing
 2-nitroimidazole compounds and methods of making such
 reagents
 INVENTOR(S): Koch, Cameron J.; Lord, Edith M.
 PATENT ASSIGNEE(S): The Trustees of the Univ. of Pennsylvania, USA; The
 University of Rochester
 SOURCE: U.S., 29 pp., Cont.-in-part of U.S. Ser. No.
 978,918, abandoned.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5540908	A	19960730	US 1994-286065	19940804
CA 2149770	AA	19940526	CA 1993-2149770	19931118
US 5843404	A	19981201	US 1996-598752	19960208
US 6252087	B1	20010626	US 1998-123300	19980728
PRIORITY APPLN. INFO.:			US 1992-978918	B2 19921119
			US 1994-286065	A3 19940804
			US 1996-598752	A2 19960208

OTHER SOURCE(S): MARPAT 125:162343

AB Novel nitroarom. compds. and immunogenic conjugates comprising a novel
 nitroarom. compd. and a carrier protein are disclosed. The invention
 further presents monoclonal antibodies highly specific for the claimed
 nitroarom. compds., protein conjugates of the compds., reductive
 byproducts of the compds., and adducts formed between the compds. and
 mammalian hypoxic cell tissue proteins. The invention is further
 directed

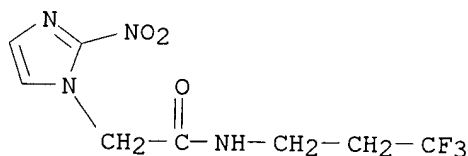
to methods for detecting tissue hypoxia using immunohistol. techniques,
 noninvasive nuclear medicine methods (PET, SPECT), or NMR. Diagnostic
 kits useful in practicing the methods of claimed invention are also
 provided.

IT 180208-73-5P

RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST
 (Analytical study); PREP (Preparation); USES (Uses)
 (hypoxia detection with 2-nitroimidazole compds. and immunogenic
 conjugates)

RN 180208-73-5 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoropropyl)- (9CI) (CA
 INDEX NAME)



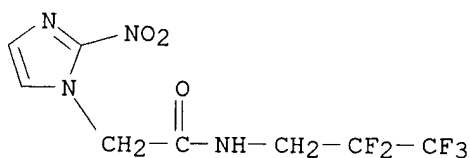
IT 152721-37-4P

RL: ARG (Analytical reagent use); SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)

(hypoxia detection with 2-nitroimidazole compds. and immunogenic conjugates)

RN 152721-37-4 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
(CA INDEX NAME)



L11 ANSWER 33 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:492707 CAPLUS

DOCUMENT NUMBER: 125:185094

TITLE: Immunocytochemical labeling of aerobic and hypoxic mammalian cells using a platinated derivative of EF5

AUTHOR(S): Matthews, J.; Adomat, H.; Farrell, N.; King, P.; Koch,

C.; Lord, E.; Palcic, B.; Poulin, N.; Sangulin, J.; Skov, K.

CORPORATE SOURCE: Department Medical Biophysics, BC Cancer Research Centre, Vancouver, BC, V5Z 1L3, Can.

SOURCE: British Journal of Cancer, Supplement (1996), 74(27), S200-S203

CODEN: BJCSB5; ISSN: 0306-9443

PUBLISHER: Stockton

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The monoclonal antibody ELK3-51 was previously developed to detect adducts

of the 2-nitroimidazole EF5. Direct immunofluorescence was used to detect

adducts of EF5 or of a platinated deriv. cis-[PtCl2(NH3)EF5] in SCCVII cells treated under aerobic or hypoxic conditions. Fluorescence measurements of these cells using both image and flow cytometric methods were compared, giving similar profiles. Platination significantly decreased immunofluorescence levels (.apprx.4-fold less than EF5) after 3 h in hypoxia, but also increased levels after exposure in air (.apprx.1.5 .times.) such that the hypoxic ratio decreased from .apprx.50 to .apprx.13. Platinated EF5 also showed significantly greater cytotoxicity than its parent in both aerobic and hypoxic cells. These results are consistent with targeting of EF5 to DNA, which was confirmed qual. by confocal microscopy.

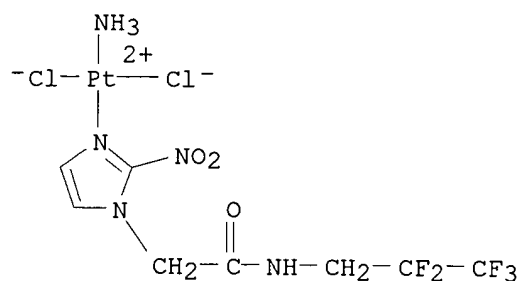
IT 180990-37-8

RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)

(immunocytochem. labeling of aerobic and hypoxic mammalian cells using a platinated deriv. of EF5)

RN 180990-37-8 CAPLUS

CN Platinum, amminedichloro[2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-1H-imidazole-1-acetamide-N3]-, (SP-4-3)- (9CI) (CA INDEX NAME)

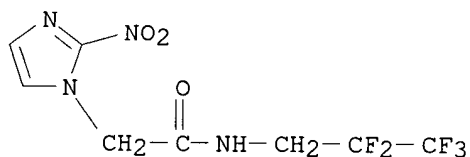


IT **152721-37-4**

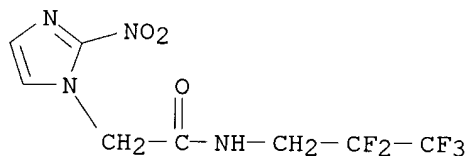
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(immunocytochem. labeling of aerobic and hypoxic mammalian cells using a platinated deriv. of EF5)

RN 152721-37-4 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
(CA INDEX NAME)



L11 ANSWER 25 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1998:589027 CAPLUS
 DOCUMENT NUMBER: 129:260386
 TITLE: An effective synthetic route to EF5
 AUTHOR(S): Baird, Ian R.; Skov, Kirsten A.; James, Brian R.;
 Rettig, Steven J.; Koch, Cameron J.
 CORPORATE SOURCE: Department of Chemistry, University of British
 Columbia, Vancouver, BC, V6T 1Z1, Can.
 SOURCE: Synthetic Communications (1998), 28(19), 3701-3709
 CODEN: SYNCAV; ISSN: 0039-7911
 PUBLISHER: Marcel Dekker, Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB EF5 (a 2-nitroimidazole contg. an N-(pentafluoropropyl)acetamide
 substituent) is a very sensitive probe for quantifying the amt. of
 hypoxia
 within cells; a much improved, short step, synthetic procedure is
 described for EF5, whose X-ray structure is also presented.
 IT **152721-37-4P**, EF5
 RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
 (prepn. of (nitroimidazolyl)(pentafluoropropyl)acetamide)
 RN 152721-37-4 CAPLUS
 CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
 (CA INDEX NAME)



L11 ANSWER 36 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:293265 CAPLUS

DOCUMENT NUMBER: 125:4533

TITLE: Biodistribution of the nitroimidazole EF5
(2-[2-nitro-1H-imidazol-1-yl]-N-(2,2,3,3,3-
pentafluoropropyl)acetamide) in mice bearing
subcutaneous EMT6 tumors

AUTHOR(S): Laughlin, K. M.; Evans, S. M.; Jenkins, W. T.; Tracy,
M.; Chan, C. Y.; Lord, E. M.; Koch, C. J.

CORPORATE SOURCE: Dep. Radn. Oncology, Univ. Pennsylvania,
Philadelphia,

PA, USA

SOURCE: Journal of Pharmacology and Experimental Therapeutics
(1996), 277(2), 1049-1057

CODEN: JPETAB; ISSN: 0022-3565

PUBLISHER: Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The characteristic redn. and binding of nitroimidazoles to cellular
macromols. in the absence of oxygen allows their use for detection and
characterization of hypoxia. The biodistribution of a new
nitroimidazole,

EF5 (2-[2-nitro-1H-imidazol-1-yl]-N-(2,2,3,3,3-
pentafluoropropyl)acetamide), in mice bearing EMT6 tumors is described.
Detection methods based on radioactivity and monoclonal antibody
techniques are compared for liver and tumor. All nonexcretory tissues
demonstrated similar levels of radioactivity at 0.5 h postinjection of
drug, demonstrating equiv. access of EF5 to all tissues. At 24 h, when
unbound drug has been cleared, the tissues with the highest binding are
the liver, esophagus, bladder and tumor. Typically, liver tissue

contains

the highest level of radio-activity at this time. Examn. of tumor and
liver tissue by use of fluorescence microscopy and Cy3-bound monoclonal
antibodies specific for EF5 adducts showed the patterns of binding in
tumor are considerably more heterogeneous than those of liver.

Histograms

of fluorescence intensity, with use of these antibodies, demonstrate av.
and maximal binding higher in tumors than in the liver. This divergence
from the radioactivity data was detd. to be unrelated to sampling error,
differential antibody access or staining efficiency of liver vs. tumor
tissue. A possible cause is the scavenging of radioactive drug
metabolites by liver. The data presented herein suggest that EF5 is
useful as a hypoxia detector and that monoclonal antibody detection
methods can give detailed information on the distribution of EF5 binding.
This technol. may allow an accurate estn. of the oxygenation and/or
nitroreductase levels in both tumor and normal tissues.

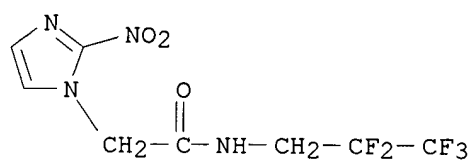
IT 152721-37-4

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)

(biodistribution of nitroimidazole EF5 in tumor and liver and other
tissues in relation to hypoxia detection)

RN 152721-37-4 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
(CA INDEX NAME)



L11 ANSWER 37 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:60562 CAPLUS

DOCUMENT NUMBER: 124:139857

TITLE: 2-Nitroimidazole (EF5) binding predicts radiation resistance in individual 9L s.c. tumors

AUTHOR(S): Evans, Sydney M.; Jenkins, W. Timothy; Joiner, Barbara; Lord, Edith M.; Koch, Cameron J.

CORPORATE SOURCE: Sch. of Veterinary Medicine, Univ. of Pennsylvania, Pennsylvania, PA, 19104, USA

SOURCE: Cancer Research (1996), 56(2), 405-11

CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The presence of hypoxic tumor cells cell is known to be an important cause

of radiation treatment resistance in vivo. The ability to predict the presence and extent of hypoxic cells in individual tumors would allow the addn. of specific "antihypoxia"-based treatment regimes. Hypoxia can be monitored by measuring the binding of 2-nitroimidazoles. We have tested the hypothesis that binding of EF5, a fluorinated deriv. of the 2-nitroimidazole, Etanidazole, can predict radioresistance in individual tumors. Fischer rats bearing 9L s.c. tumors were given injections i.v. with EF5 3 h before irradiation and tumor harvest. Tumor cells were dissociated for flow cytometric analysis and plating efficiency studies. EF5 binding

was

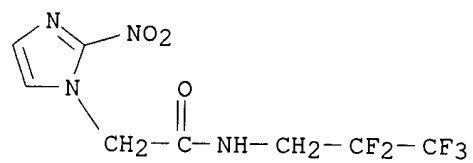
detected via monoclonal antibodies conjugated to the orange emitting dye, Cy3. In air breathing rats, for a given radiation dose, a large amount of variation in plating efficiency was seen. However, there was minimal variability of the plating efficiency for tumors irradiated in euthanized animals (hypoxic tumors; correlation coefficient for the fitted curve = 0.93) and in cells dissociated from tumors and irradiated in suspension (correlation coefficient for the fitted curve = 0.99), suggesting that varying sensitivity to the cell disaggregation technique was not responsible. In contrast, a good correlation between the relative radiation resistance or hypoxic survival and EF5 binding of "moderately" hypoxic cells in air breathing rats was identified using these techniques. In these 9L s.c. tumors, intertumor variation in oxygenation accounted for most of the range in individual tumor radiation response, and this was found to be independent of tumor size. This study provides evidence for the application of EF5 binding with monoclonal antibody detection as an in vivo predictive assay of individual tumor hypoxia and resultant therapy resistance.

IT 152721-37-4

RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses) (2-nitroimidazole (EF5) binding to tumor hypoxic fractions predicts x-ray resistance in individual 9L s.c. tumors)

RN 152721-37-4 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)



L11 ANSWER 49 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:101090 CAPLUS

DOCUMENT NUMBER: 120:101090

TITLE: Detection of hypoxic cells by monoclonal antibody recognizing 2-nitroimidazole adducts

AUTHOR(S): Lord, Edith M.; Harwell, Lee; Koch, Cameron J.

CORPORATE SOURCE: Cancer Cent., Univ. Rochester, Rochester, NY, 14642, USA

SOURCE: Cancer Research (1993), 53(23), 5721-6

CODEN: CNREA8; ISSN: 0008-5472

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A pentafluorinated deriv. [EF5;

2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-

pentafluoropropyl)acetamide] of etanidazole was synthesized with the expectation of lessening some of the non-oxygen-dependent variability in adduct formation obsd. previously with other nitroarom. compds.

EF5-protein conjugates, prepd. by radiochem. redn., were found to be immunogenic and allowed the development of monoclonal antibodies. One of these antibodies, ELK2-4, has been characterized and found to be highly specific for the EF5 adducts whether produced radiochem. or by cellular bioreductive metab. The 9L rat glioma cells pretreated with EF5 under hypoxic, compared with aerobic, conditions were readily discriminated immunochem. using fluorochrome-conjugated secondary antibodies which recognize the ELK2-4 antibody subtype (IgG1). Similarly, the central region of multicellular spheroids, composed of EMT6 mouse mammary sarcoma cells, was selectively visualized by immunohistochem. after the spheroids were incubated for 4 h in 0.5 mM EF5. Tumor biopsy, prepn., and immunohistochem. staining 24 h after treatment of tumor-bearing animals with drug also demonstrated high contrast regions within EMT6 mouse or Morris 7777 hepatoma rat tumors. The use of this new compd. and its highly specific monoclonal antibody may allow elucidation of bioreductive metab. of the nitroheterocyclics and significantly improve technologies for the quantitation of tissue pO₂.

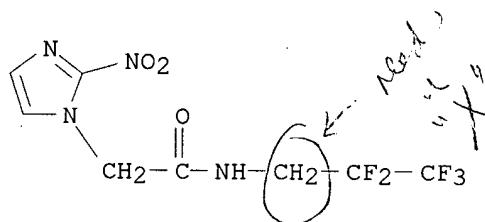
IT 152721-37-4

RL: ANST (Analytical study)

(in hypoxic cell detection with monoclonal antibodies)

RN 152721-37-4 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
(CA INDEX NAME)



L11 ANSWER 39 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:936067 CAPLUS

DOCUMENT NUMBER: 124:44585

TITLE: Identification of hypoxia in cells and tissues of
epigastric 9L rat glioma using EF5
[2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-
pentafluoropropyl) acetamide]

AUTHOR(S): Evans, S M.; Joiner, B.; Jenkins, W T.; Laughlin, K
M.; Lord, E M.; Koch, C J.

CORPORATE SOURCE: Schools Veterinary Medicine (Clinical Studies),

University Pennsylvania, Philadelphia, PA, 19104, USA

SOURCE: British Journal of Cancer (1995), 72(4), 875-82

CODEN: BJCAAI; ISSN: 0007-0920

PUBLISHER: Macmillan Scientific & Medical Division

DOCUMENT TYPE: Journal

LANGUAGE: English

AB One of the most sensitive hypoxia detection methods is based on the observation that binding of nitroimidazoles to cellular macromols. occurs as a result of hypoxia-dependent bioeredn. by cellular nitroreductases. Nitroimidazole-binding techniques provide measurements of hypoxia to virtually and degree of spatial resohn. and with a multiplicity of techniques. This paper demonstrates hypoxia imaging using in vivo EF5 binding with detection by a fluorochrome-conjugated monoclonal antibody. The authors investigated these techniques in the 9L glioma tumor, in part because the exact nature of the hypoxia in this tumor system is controversial. The results demonstrate that following i.v. injection of EF5, binding and detection using a monoclonal antibody in 9L gliomas is specific and oxygen dependent. Detection of binding using fluorescence microscopy can be performed on frozen tissues; tissue sections can be counterstained with haematoxylin and eosine for light microscopic anal. Alternatively, the distribution of hypoxia in a tumor can be inferred by examg. individual tumor cells using flow cytometric techniques. Based upon the results presented herein, the radiation-resistant phenotype of

9L epigastric tumors grown in the labs. can be assocd. with the presence of hypoxic cells.

IT 152721-37-4

RL: BAC (Biological activity or effector, except adverse); BSU

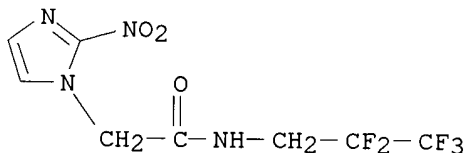
(Biological

study, unclassified); BIOL (Biological study)

(identification of hypoxia in cells and tissues of epigastric 9L rat glioma using EF5 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl) acetamide])

RN 152721-37-4 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
(CA INDEX NAME)



L11 ANSWER 38 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:1002637 CAPLUS

DOCUMENT NUMBER: 124:52283

TITLE: Mapping of the vascular endothelial growth factor-producing hypoxic cells in multicellular tumor spheroids using a hypoxia-specific marker

AUTHOR(S): Waleh, Nahid S.; Brody, Michael D.; Knapp, Merrill A.;

CORPORATE SOURCE: Mendonca, Holly L.; Lord, Edith M.; Koch, Cameron J.; Laderoute, Keith R.; Sutherland, Robert M. Cellular and Mol. Biol. Lab., Life Sci. Div., Menlo Park, CA, 94025, USA

SOURCE: Cancer Research (1995), 55(24), 6222-6
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: American Association for Cancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The authors have investigated the hypoxia inducibility of vascular endothelial growth factor (VEGF) in multicellular tumor spheroids of HT29 cells using a monoclonal antibody to a fluorinated bioreductive drug, EF5 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide],

a chem. probe for hypoxia. The authors have shown that VEGF expression is predominantly localized in interior spheroid cells that are sufficiently hypoxic to bioreductively activate the 2-nitroimidazole and produce immunol. detectable adducts of the EF5 compd. Northern blotting analyses demonstrated that VEGF165 is the predominant form of VEGF produced by

HT29 cells and that the phorbol ester 12-O-tetradecanoylphorbol-13-acetate did not induce VEGF expression. This study demonstrates that VEGF expression is up-regulated in response to hypoxia and in the microenvironments found in human multicellular tumor spheroids. This investigation also illustrates the utility of the EF5 binding in multicellular tumor spheroids as a means of studying the expression and regulation of hypoxia-inducible genes.

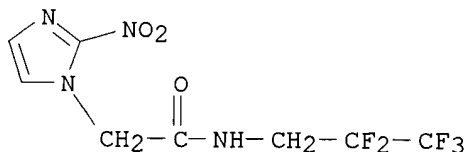
IT 152721-37-4

RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(vascular endothelial growth factor expression colocalization with EF5 binding in hypoxic regions of multicellular tumor spheroids of human HT29 cells)

RN 152721-37-4 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
(CA INDEX NAME)



L11 ANSWER 40 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:936066 CAPLUS

DOCUMENT NUMBER: 124:44665

TITLE: Oxygen dependence of cellular uptake of EF5
[2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide]: Analysis of drug

adducts

by fluorescent antibodies vs. bound radioactivity
AUTHOR(S): Koch, C. J.; Evans, S. M.; Lord, E. M.

CORPORATE SOURCE: Radiation Oncology, University Pennsylvania,
Philadelphia, PA, 19104-6072, USA

SOURCE: British Journal of Cancer (1995), 72(4), 869-74
CODEN: BJCAAI; ISSN: 0007-0920

PUBLISHER: Macmillan Scientific & Medical Division

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The present studies were initiated to quantitate the oxygen dependence of bioreductive metab.-induced binding of EF5, a pentafluorinated deriv. of the 2-nitroimidazole, etanidazole. Two different assays were compared: first, radioactive drug incorporation into cell lysates, which provides a direct measure of drug metab. or uptake; second, monoclonal antibody detection of cellular macromol. adducts of EF5 after whole cell permeabilization and fixing. The antibodies (a single clone designated ELK3-5I) were conjugated with the fluorescent dye Cy3, with fluorescence detd. by fluorescence microscopy and flow cytometry. For the two cell lines tested (V79 Chinese hamster fibroblasts and 9L rat glioma), the oxygen dependence of binding was the same for the two techniques. Using the antibody binding technique, the fluorescence signal was highly reproducible between expts., resistant to light or chem. bleaching and stable over time following cell or tissue staining. Flow cytometric

anal.

of cells from rat 9L tumors treated with EF5 in vivo or in vitro showed a distribution of fluorescent signal which was very compatible, on both a relative and abs. basis, with the in vitro results. The results indicate that immunofluorescent techniques provide a quant. assay for bioreductive drug adducts, and therefore may be able to measure the abs. oxygen concn. distribution in cell populations and tissues of interest.

IT 152721-37-4

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

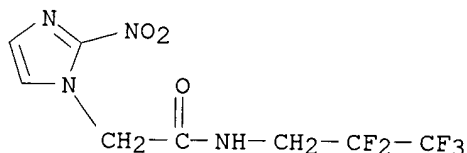
(oxygen dependence of cellular uptake of EF5
[2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide]: anal. of drug adducts

by

fluorescent antibodies vs. bound radioactivity)

RN 152721-37-4 CAPLUS

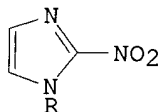
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
(CA INDEX NAME)



L11 ANSWER 51 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1991:6504 CAPLUS
DOCUMENT NUMBER: 114:6504
TITLE: Preparation of 3-(2-nitroimidazolo)-2,2-difluoropropionamides and analogs as radiosensitizers
INVENTOR(S): Kagiya, Tsutomu; Abe, Mitsuyuki; Nishimoto, Seiichi; Shibamoto, Yuta; Otomo, Susumu; Tanami, Tooru; Shimokawa, Kazuhiro; Yoshizawa, Toru; Hisanaga, Yorisato
PATENT ASSIGNEE(S): Nishijima, Yasunori, Japan; Taisho Pharmaceutical Co., Ltd.; Daikin Industries, Ltd.
SOURCE: Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 373630	A1	19900620	EP 1989-123062	19891213
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 2005261	AA	19900614	CA 1989-2005261	19891212
US 4977273	A	19901211	US 1989-448909	19891212
AU 8946713	A1	19900621	AU 1989-46713	19891213
AU 625581	B2	19920716		
ZA 8909503	A	19900926	ZA 1989-9503	19891213
JP 02275863	A2	19901109	JP 1989-325437	19891214
PRIORITY APPLN. INFO.:			JP 1988-315974	19881214
OTHER SOURCE(S):			CASREACT 114:6504; MARPAT 114:6504	
GI				

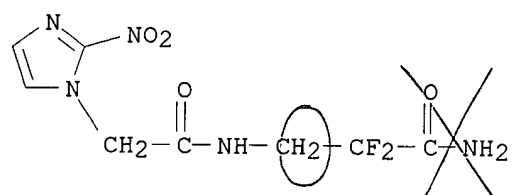


AB The title compds. [I; R = CH₂CFXCH₂OR₁; R₁ = CH₂CH(OR₂)CH₂OR₂, (CH₂)_lOR₂, (CH₂)_lCOR₂, (CH₂)_m(CF₂)_n[CONH(CHR₃)_r(CF₂)_p]qZ, etc.; R₂ = H, OH (sic), alkyl, acyl; R₂₂ = PhCH, Me₂C; R₃ = H, alkyl; X = H, halo; Z = H, CO₂R₃, CO₂H, CONH₂, etc.; l = 1-3; m, n = 0-4; p = 0-2; q, r = 0-3] were prepd. as hypoxic cell sensitizers. Thus, I (R = CH₂CF₂CO₂Me) was stirred 1 h with H₂NCH₂CH₂CO₂Me.HCl in MeOH contg. KOH and the product stirred 2 days with aq. NH₃-MeOH contg. KOH to give I (R = CH₂CF₂CONHCH₂CH₂CONH₂) which gave cell-survival rate of EMT-6 tumor cells X-irradiated in mouse thigh 66% that of unirradiated cells after administration of 100 mg/kg i.p.

IT **130777-35-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as radiosensitizer)

RN 130777-35-4 CAPLUS

CN 1H-Imidazole-1-acetamide, N-(3-amino-2,2-difluoro-3-oxopropyl)-2-nitro-(9CI) (CA INDEX NAME)



Connecting via Winsock to STN

Welcome to STN International! Enter x:X

LOGINID:sssptal626amd

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * Welcome to STN International * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2	Apr 08	"Ask CAS" for self-help around the clock
NEWS	3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS	4	Apr 09	ZDB will be removed from STN
NEWS	5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and IFIUDB
NEWS	6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS	7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS	8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS	9	Jun 03	New e-mail delivery for search results now available
NEWS	10	Jun 10	MEDLINE Reload
NEWS	11	Jun 10	PCTFULL has been reloaded
NEWS	12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS	13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS	14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS	15	Jul 30	NETFIRST to be removed from STN
NEWS	16	Aug 08	CANCERLIT reload
NEWS	17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS	18	Aug 08	NTIS has been reloaded and enhanced
NEWS	19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS	20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS	21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS	22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS	23	Sep 03	JAPIO has been reloaded and enhanced
NEWS	24	Sep 16	Experimental properties added to the REGISTRY file
NEWS	25	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS	26	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS	27	Oct 21	EVENTLINE has been reloaded
NEWS	28	Oct 24	BEILSTEIN adds new search fields
NEWS	29	Oct 24	Nutraceuticals International (NUTRACEUT) now available on STN
NEWS	30	Oct 25	MEDLINE SDI run of October 8, 2002
NEWS	31	Nov 18	DKILIT has been renamed APOLLIT
NEWS	32	Nov 25	More calculated properties added to REGISTRY
NEWS	33	Dec 02	TIBKAT will be removed from STN
NEWS	34	Dec 04	CSA files on STN
NEWS	35	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS	36	Dec 17	TOXCENTER enhanced with additional content
NEWS	37	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS	38	Dec 30	ISMEC no longer available

NEWS 39 Jan 13 Indexing added to some pre-1967 records in CA/CAPLUS
NEWS 40 Jan 21 NUTRACEUT offering one free connect hour in February 2003
NEWS 41 Jan 21 PHARMAML offering one free connect hour in February 2003
NEWS 42 Jan 29 Simultaneous left and right truncation added to COMPENDEX,
ENERGY, INSPEC

NEWS EXPRESS January 6 CURRENT WINDOWS VERSION IS V6.01a,
CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP),
AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS INTER General Internet Information
NEWS LOGIN Welcome Banner and News Items
NEWS PHONE Direct Dial and Telecommunication Network Access to STN
NEWS WWW CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

* * * * * STN Columbus * * * * *

FILE 'HOME' ENTERED AT 16:06:31 ON 12 FEB 2003

=> fil reg

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.21	0.21

FULL ESTIMATED COST

FILE 'REGISTRY' ENTERED AT 16:06:38 ON 12 FEB 2003

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

COPYRIGHT (C) 2003 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 11 FEB 2003 HIGHEST RN 488780-79-6

DICTIONARY FILE UPDATES: 11 FEB 2003 HIGHEST RN 488780-79-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:

<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=>

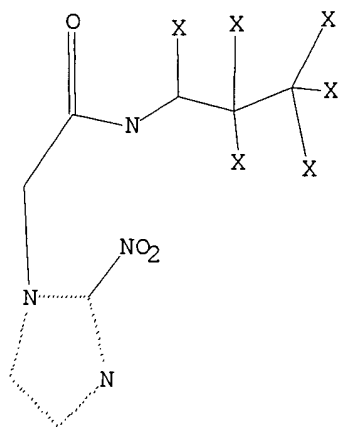
Uploading 10049284.str

L1 STRUCTURE UPLOADED

=> d

L1 HAS NO ANSWERS

L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l1 ful

FULL SEARCH INITIATED 16:06:54 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 13 TO ITERATE

100.0% PROCESSED 13 ITERATIONS

0 ANSWERS

SEARCH TIME: 00.00.01

L2 0 SEA SSS FUL L1

=>

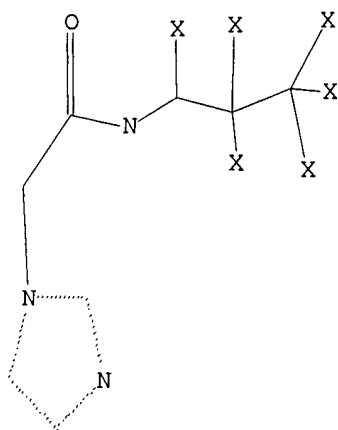
Uploading 10049284.str

L3 STRUCTURE UPLOADED

=> d

L3 HAS NO ANSWERS

L3 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l3 ful

FULL SEARCH INITIATED 16:07:25 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 3 TO ITERATE

100.0% PROCESSED 3 ITERATIONS

0 ANSWERS

SEARCH TIME: 00.00.02

L4 0 SEA SSS FUL L3

=>

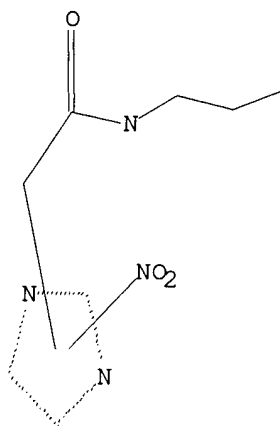
Uploading 10049284.str

L5 STRUCTURE UPLOADED

=> d

L5 HAS NO ANSWERS

L5 STR



Structure attributes must be viewed using STN Express query preparation.

=> s 15 ful
FULL SEARCH INITIATED 16:09:03 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 6926 TO ITERATE

100.0% PROCESSED 6926 ITERATIONS
SEARCH TIME: 00.00.01

91 ANSWERS

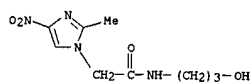
L6 91 SEA SSS FUL L5

=> s 16 and caplus/lc
26154954 CAPLUS/LC
L7 88 L6 AND CAPLUS/LC

=> s 16 not 17
L8 3 L6 NOT L7

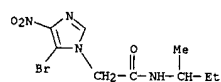
=> d 1-3

L8 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2003 ACS
 RN 405279-27-8 REGISTRY
 CN 1H-Imidazole-1-acetamide, N-(3-hydroxypropyl)-2-methyl-4-nitro- (9CI)
 (CA)
 FS INDEX NAME)
 MF 3D CONCORD
 MF C9 H14 N4 O4
 SR Chemical Library
 LC STN Files: CHEMCATS



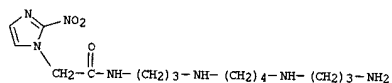
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L8 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2003 ACS
 RN 362596-32-5 REGISTRY
 CN 1H-Imidazole-1-acetamide, 5-bromo-N-(1-methylpropyl)-4-nitro- (9CI)
 (CA)
 FS INDEX NAME)
 MF 3D CONCORD
 MF C9 H13 Br N4 O3
 SR Chemical Library
 LC STN Files: CHEMCATS



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L8 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2003 ACS
 RN 165062-81-7 REGISTRY
 CN 1H-Imidazole-1-acetamide,
 N-{3-[[4-[(3-aminopropyl)amino]butyl]amino]propyl-
 1}-2-nitro- (9CI) (CA INDEX NAME)
 FS 3D CONCORD
 MF C15 H29 N7 O3
 CI COM
 SR CA



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

=>

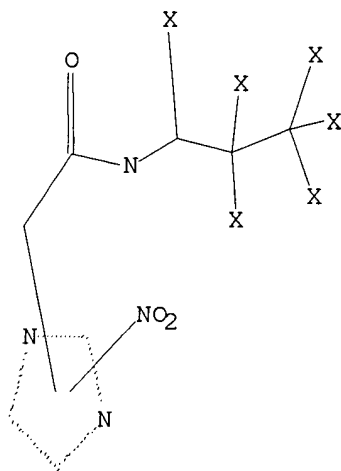
Uploading 10049284.str

L9 STRUCTURE UPLOADED

=> d

L9 HAS NO ANSWERS

L9 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l9 ful

FULL SEARCH INITIATED 16:10:06 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 11 TO ITERATE

100.0% PROCESSED 11 ITERATIONS

0 ANSWERS

SEARCH TIME: 00.00.01

L10 0 SEA SSS FUL L9

=> fil caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

602.66

602.87

FILE 'CAPLUS' ENTERED AT 16:10:17 ON 12 FEB 2003

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available

for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 12 Feb 2003 VOL 138 ISS 7
FILE LAST UPDATED: 11 Feb 2003 (20030211/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d his

(FILE 'HOME' ENTERED AT 16:06:31 ON 12 FEB 2003)

FILE 'REGISTRY' ENTERED AT 16:06:38 ON 12 FEB 2003

L1	STRUCTURE UPLOADED
L2	0 S L1 FUL
L3	STRUCTURE UPLOADED
L4	0 S L3 FUL
L5	STRUCTURE UPLOADED
L6	91 S L5 FUL
L7	88 S L6 AND CAPLUS/LC
L8	3 S L6 NOT L7
L9	STRUCTURE UPLOADED
L10	0 S L9 FUL

FILE 'CAPLUS' ENTERED AT 16:10:17 ON 12 FEB 2003

=> s 16

L11 62 L6

=> d 1-62 ibib abs hitstr

L11 ANSWER 1 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:526269 CAPLUS

DOCUMENT NUMBER: 137:292513

TITLE: Effects of hyperglycemia on oxygenation, radiosensitivity and bioenergetic status of subcutaneous RIF-1 tumors
AUTHOR(S): Nadal-Desbarats, L.; Poptani, H.; Oprysko, P.; Jenkins, W. T.; Busch, T. M.; Nelson, D. S.;

Glickson,

J. D.; Koch, C. J.; Evans, S. M.
CORPORATE SOURCE: Department of Radiology, University of Pennsylvania,

Philadelphia, PA, 19104, USA
SOURCE: International Journal of Oncology (2002), 21(1), 103-110

CODEN: IJONES; ISSN: 1019-6439

PUBLISHER: International Journal of Oncology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Since tissue O tension is a balance between delivery and consumption of O,

considerable effort was directed at increasing the former and/or decreasing the latter. Techniques to decrease the rate of cellular O consumption (increasing the distance O can diffuse into tissues)

include increasing glycolysis by administering supraphysiol. levels of glucose.

We have examd. the effect of hyperglycemia produced by i.v. glucose infusion on the tissue oxygenation and radiation response of s.c. implanted murine radiation induced fibrosarcomas (RIF-1). A 0.3 M

glucose soln. was delivered via tail vein injection according to a protocol that

maintained glucose at a plasma concn. of 17.+-1 mM. The effect of this treatment on radiation response (clonogenic and growth delay

studies), tumor oxygenation (needle electrode pO2 and 2-[2-nitro-1H-imidazol-1-yl]-N-

(2,2,3,3,3-pentafluoropropyl) acetamide (EF5) binding), and tumor bioenergetics and pH (31P NMR spectroscopy) was examd. Systemic

measurements included hematocrit and blood glucose and lactate concns. The results of these studies suggest that these s.c. implanted RIF-1 tumors are both radiobiol. and metabolically hypoxic and that i.v.

glucose infusion is not an effective method of modifying this metabolic state

IT 152721-37-4, EF5

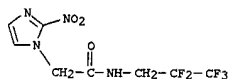
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses) (hyperglycemia effect on oxygenation, radiosensitivity, and EF5

binding in s.c. RIF-1 tumors)

RN 152721-37-4 CAPLUS

CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
(CA INDEX NAME)

L11 ANSWER 1 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS

FORMAT RECORD. ALL CITATIONS AVAILABLE IN THE RE

L11 ANSWER 2 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:446905 CAPLUS

DOCUMENT NUMBER: 138:66150

TITLE: Modeling of the anticancer action for radical derivatives of nitroazoles: quantitative structure-activity relationship (QSAR) study
AUTHOR(S): Khebnikov, Andrei; Schepetkin, Igor; Se Kwon,

Byoung

CORPORATE SOURCE: Altai State Technical University, Barnaul, Russia
SOURCE: Cancer Biotherapy & Radiopharmaceuticals (2002), 17(2), 193-203

CODEN: CBRAFJ; ISSN: 1084-9785

PUBLISHER: Mary Ann Liebert, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A QSAR anal. of the anti-tumor, anti-metastasis and anti-colony formation

(for metastatic colonies) activities of eighteen nitroazoles

(including metronidazole and hypoxic radiosensitizers RP-170, KU-2285 and

sanazole (drug AK-2123)) and their nitro and nitroso anion radical derivs.

against melanoma B16 in mice has been performed. The QSAR models were built

with the use of the frontal polygon method. This approach has features of

different 3D QSAR methodologies and belongs to the group of

"indirect" methods. The procedure allows to build robust models with high

predictive ability even in series of diverse and conformationally flexible

compsds. Key at. characteristics accompany the geometrical requirements in the

anal. of local 3D mol. similarity. By variation of wt. coeffs. for

hydrophobicity, refraction increments, and partial charge it is

possible to achieve better quality of QSAR and evaluate the importance of each

characteristic for biol. activity under consideration. It was found

that hydrophobicity, molar refraction and charge characteristics of nitro

anion radical derivs. are more significant for interaction with mol.

targets than those of the parent compds. and of the nitroso anion radical

derivs. Size and hydrophobic properties of substituents in nitro anion

radicals play significant role for ligand-target interaction in the processes

of inhibition of metastatic spreading and growth of metastatic colonies

by nitroazoles. A scheme of competitive interaction of parent

nitroazoles and their anion radicals with a target in organism is suggested. It

can be concluded that the step of one-electron redn. of nitroazoles can

be

L11 ANSWER 2 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

important for anticancer activity of these drugs.

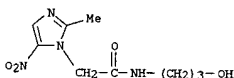
IT 205811-49-0

RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (modeling of anticancer action for radical derivs. of nitroazoles

and their quant. structure-activity relationship (QSAR))

RN 205811-49-0 CAPLUS

CN 1H-Imidazole-1-acetamide, N-(3-hydroxypropyl)-2-methyl-5-nitro- (9CI)
(CA INDEX NAME)

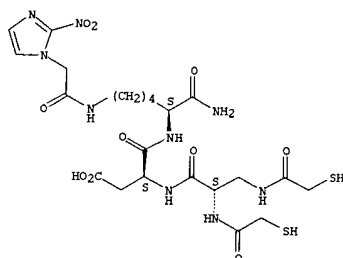


REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS

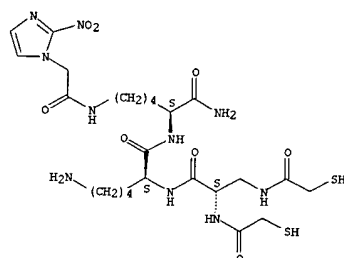
FORMAT RECORD. ALL CITATIONS AVAILABLE IN THE RE

$$\begin{array}{c} \text{PhCO-S-CH}_2\text{-CO-NH} \quad \text{CO-Xaa-L-Lys-NH(Resin)} \\ | \\ \text{PhCO-S-CH}_2\text{-CO-NH} \quad \text{CO} \\ | \\ \text{H}_2\text{C-N} \quad \text{N} \\ | \quad \quad \quad | \\ \text{O}_2\text{N} \quad \quad \quad \text{N} \end{array}$$

L11 ANSWER 3 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



Absolute stereochemistry.

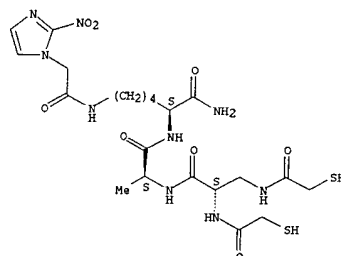


Absolute stereochemistry.

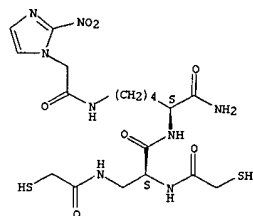
Absolute stereochemistry.

O=[N+]([O-])c1ccn(c1)CC(=O)NC(CS(=O)(=O)NC(=O)CNC(=O)CS)CCCCNC(=O)CNC(=O)CS

Absolute stereochemistry.

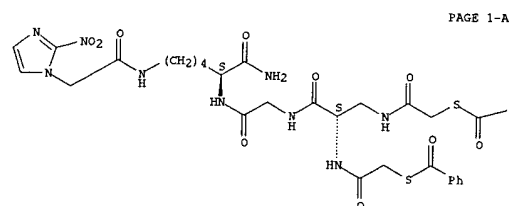


Absolute stereochemistry.

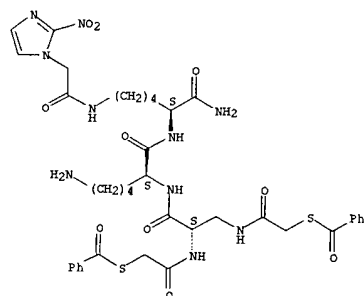


IT 422309-53-3P 422309-54-4P 422309-55-5P
 422309-56-6P 422309-57-7P 422309-58-8P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
 RACT (Reactant or reagent)
 (solid-phase prepn. of peptides contg. a protected diaminedithiol
 chelator for 99Tc)
 RN 422309-53-3 CAPLUS
 CN L-Lysinamide,
 N-[(benzoylthio)acetyl]-3-[(benzoylthio)acetyl]amino]-L-
 alanyl-L-lysyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX
 NAME)

Absolute stereochemistry.

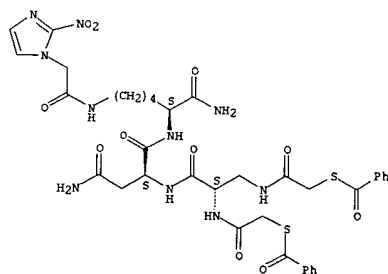


PAGE 1-A



RN 422309-56-6 CAPLUS
 CN L-Lysinamide,
 N-[(benzoylthio)acetyl]-3-[(benzoylthio)acetyl]amino]-L-
 alanyl-L-asparaginy-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI)
 (CA INDEX NAME)

Absolute stereochemistry.

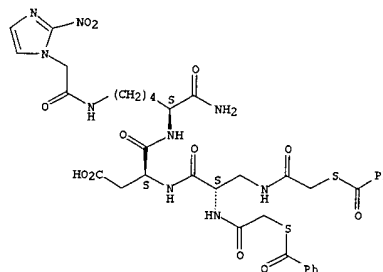


RN 422309-57-7 CAPLUS
 CN L-Lysinamide,
 N-[(benzoylthio)acetyl]-3-[(benzoylthio)acetyl]amino]-L-

Ph

RN 422309-54-4 CAPLUS
 CN L-Lysinamide,
 N-[(benzoylthio)acetyl]-3-[(benzoylthio)acetyl]amino]-L-
 alanyl-L- α -aspartyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI)
 (CA INDEX NAME)

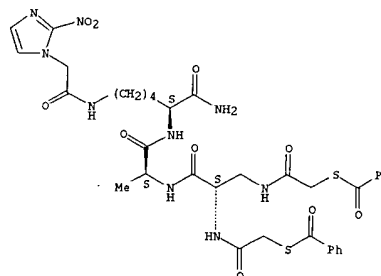
Absolute stereochemistry.



RN 422309-55-5 CAPLUS
 CN L-Lysinamide,
 N-[(benzoylthio)acetyl]-3-[(benzoylthio)acetyl]amino]-L-
 alanyl-L-lysyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX
 NAME)

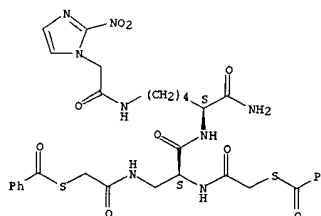
Absolute stereochemistry.

Absolute stereochemistry.



RN 422309-58-8 CAPLUS
 CN L-Lysinamide,
 N-[(benzoylthio)acetyl]-3-[(benzoylthio)acetyl]amino]-L-
 alanyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX NAME)

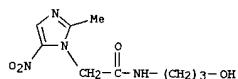
Absolute stereochemistry.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR
 THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
 FORMAT

L11 ANSWER 4 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 2002:109891 CAPLUS
 DOCUMENT NUMBER: 137:163307
 TITLE: Quantitative structure-activity relationships
 (QSAR) for antitumor activity of nitroazoles: A
 comparative analysis for the parent compounds and their nitro anion radical and nitroso anion radical
 derivatives
 AUTHOR(S): Khlebnikov, Andrei; Schepetkin, Igor; Kim, Byung Sam;
 CORPORATE SOURCE: Kwon, Byoung Se
 Altai State Technical University, Barnaul, 656099, Russia
 SOURCE: Proceedings - KORUS 2001, the Korea-Russia International Symposium on Science and Technology, 5th, Tomsk, Russian Federation, June 26-July 3, 2001
 and (2001), Volume 3, 10-14. Institute of Electrical Electronics Engineers: New York, N. Y.
 CODEN: 69CGH4; ISBN: 0-7803-7008-2
 DOCUMENT TYPE: Conference
 LANGUAGE: English
 AB A QSAR anal. of the antitumor, antimetastatic and anti-colony formation (for metastatic colonies) activities of eighteen nitroazoles and their nitro anion radical and nitroso anion radical derivs. against melanoma B16 in mice is reported. The QSAR models were built with the use of the frontal polygon method. This approach has features of different 3D QSAR methodologies. The procedure allows to build robust models with high predictive ability even in series of diverse and conformationally flexible compds. Key at. characteristics (hydrophobicity and refraction increments, partial charge) accompany the geometrical requirements in the anal. of local 3D mol. similarity. By variation of wt. coeffs. for these properties it is possible to achieve better quality of QSAR and evaluate the importance of each characteristic for biol. activity under consideration. It is the evidence that hydrophobicity, molar refraction and charge characteristics of nitro anion radical derivs. are more significant for interaction with mol. targets than those of the parent compds. and of the nitroso anion radical derivs. Thus, the step of one-electron redn. of nitroazoles can be important for antitumor, anti-metastatic and anti-colony formation activity of these drugs.
 IT 205811-49-0
 RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (QSAR for antitumor activity of nitroazoles and corresponding nitro- and nitroso-anion radicals)

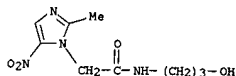
L11 ANSWER 4 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 RN 205811-49-0 CAPLUS
 CN 1H-imidazole-1-acetamide, N-(3-hydroxypropyl)-2-methyl-5-nitro-
 (9CI) (CA
 INDEX NAME)



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE
 FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
 FORMAT

L11 ANSWER 5 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 2002:109829 CAPLUS
 DOCUMENT NUMBER: 137:179366
 TITLE: Quantitative structure-activity relationships
 (QSAR) for antitumor activity of nitroazoles: A
 comparative analysis for the parent compounds and their nitro anion radical and nitroso anion radical
 derivatives
 AUTHOR(S): Khlebnikov, Andrei; Schepetkin, Igor; Kim, Byung Sam;
 CORPORATE SOURCE: Kwon, Byoung Se
 Altai State Technical University, Barnaul, 656099, Russia
 SOURCE: Proceedings - KORUS 2001, the Korea-Russia International Symposium on Science and Technology, 5th, Tomsk, Russian Federation, June 26-July 3, 2001
 and (2001), Volume 2, 58-62. Institute of Electrical Electronics Engineers: New York, N. Y.
 CODEN: 69CGH4; ISBN: 0-7803-7008-2
 DOCUMENT TYPE: Conference
 LANGUAGE: English
 AB QSAR anal. of the antitumor, antimetastatic and anti-colony formation (for metastatic colonies) activities of eighteen nitroazoles and their nitro anion radical and nitroso anion radical derivs. against melanoma B16 in mice is reported. The QSAR models were built with the use of the frontal polygon method. This approach has features of different 3D QSAR methodologies. The procedure allows to build robust models with high predictive ability even in series of diverse and conformationally flexible compds. Key at. characteristics (hydrophobicity and refraction increments, partial charge) accompany the geometrical requirements in the anal. of local 3D mol. similarity. It was found that characteristics of nitro anion radical derivs. are more significant for interaction with mol. targets than those of the parent compds. and of the nitroso anion radical derivs. Thus, the step of one-electron redn. of nitroazoles can be important for antitumor, antimetastatic and anti-colony formation activity of these drugs.
 IT 205811-49-0
 RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (quant. structure-activity relationships (QSAR) for antitumor activity of nitroazoles and a comparative anal. for parent compds. and nitro anion radical and nitroso anion radical derivs.)

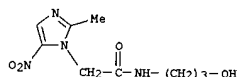
L11 ANSWER 5 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
RN 205811-49-0 CAPLUS
CN 1H-imidazole-1-acetamide, N-(3-hydroxypropyl)-2-methyl-5-nitro-
(9CI) (CA
INDEX NAME)



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L11 ANSWER 6 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:54934 CAPLUS
DOCUMENT NUMBER: 136:288539
TITLE: Quantitative structure-activity relationships for
nitroazoles with antitumor activity
AUTHOR(S): Khlebnikov, A. I.; Shchepetkin, I. A.;
Akmedzhanov, R. R.
CORPORATE SOURCE: Altai State Technical University, Barnaul, Russia
SOURCE: Pharmaceutical Chemistry Journal (Translation of
Khimiko-Farmatsevticheskii Zhurnal) (2001), 35(6),
315-320
CODEN: PCJOAU; ISSN: 0091-150X
PUBLISHER: Kluwer Academic/Consultants Bureau
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The frontal polyhedra method was used to analyze the quant.
structure-activity relation (QSAR) of nitroazoles with known
antitumor,
antimetastatic, and colony-inhibiting properties that were previously
established within the framework of the exptl. model of melanoma B-16.
The roles of various factors involved in the mol. recognition and the
extent of participation of various structural fragments of mols. in
the manifestation of these types of activity were studied. QSAR models
were constructed for each of the biol. types studied. The base QSAR
equations
obtained for the no. of min. assignments in the optimum
superimpositions
(N0) and optimum boundary criterion (K0) values selected 3 and 0.10,
resp., were optimized by sequential twofold reduct. in the weighing
coeffs.
The difference in contributions of substituents, primarily of the
azole
heterocycle and nitro group, to the biol. activity manifestations for
nitroazoles probably indicates the existence of different mol. targets
(receptors) involved in the antitumor, antimetastatic, and
colony-inhibiting interactions. The role of such targets can be
played by
enzymes possessing nitroreductase activity, by various surface and
intracellular receptors.
IT 205811-49-0
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic
use); BIOL (Biological study); USES (Uses)
(QSAR of nitroazoles with antitumor activity)
RN 205811-49-0 CAPLUS
CN 1H-imidazole-1-acetamide, N-(3-hydroxypropyl)-2-methyl-5-nitro- (9CI)
(CA
INDEX NAME)

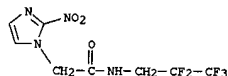
L11 ANSWER 6 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L11 ANSWER 7 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:790212 CAPLUS
DOCUMENT NUMBER: 136:67942
TITLE: Hypoxia-inducible factor-1.alpha. is an intrinsic
marker for hypoxia in cervical cancer xenografts
Vukovic, Vojislav; Haugland, Hans Kristian;
Nickless, Trudey; Morrison, Andrew J.; Hedley, David W.
CORPORATE SOURCE: Departments of Medical Biophysics, Ontario Cancer
Institute/Princess Margaret Hospital, Toronto,
ON, M5G
SOURCE: 2M9, Can.
Cancer Research (2001), 61(20), 7394-7398
CODEN: CNREAS; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The hypoxia-inducible factor 1 (HIF-1) is known to induce the
expression
of several proteins linked to the maintenance of oxygen homeostasis,
cellular energy metab., and tumor progression. Its .alpha. subunit
(HIF-1.alpha.) is stabilized under hypoxic conditions and, therefore,
might represent an intrinsic marker for tissue hypoxia. Here we
report
on the spatial relationship between HIF-1.alpha. and the
nitroimidazole
hypoxia marker EF5 in cervical carcinoma xenografts, and on their
spatial
relationship to tumor blood vessels. EF5 was administered to mice
bearing
ME180 and SiHa cervical cancer xenografts. Frozen tumor tissue
sections,
triple-stained for HIF-1.alpha., the endothelial cell marker CD31, and
EF5, were imaged using wide-field multiparameter immunofluorescence
microscopy. Expression levels of EF5 and HIF-1.alpha. were similar in
ME180 xenografts, but the percentage of tumor area stained with EF5
was
significantly smaller than the percentage of HIF-1.alpha.-pos. area in
SiHa tumors. In both tumor types the EF5-HIF-1.alpha. overlap was
statistically significant, thus confirming their spatial and temporal
colocalization. Spatial distribution anal. of EF5 and HIF-1.alpha. is
consistent with different pO₂ value "thresholds" for EF5 binding and
HIF-1.alpha. expression. Summarized, our results indicate that
HIF-1.alpha. is a useful intrinsic marker for hypoxia in cervical
carcinoma xenografts.
IT 152721-37-4
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL
(Biological study); USES (Uses)
(hypoxia-inducible factor-1.alpha. as intrinsic marker for hypoxia
in
cervical carcinoma xenografts)
RN 152721-37-4 CAPLUS
CN 1H-imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-
(9CI)
(CA INDEX NAME)

L11 ANSWER 7 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

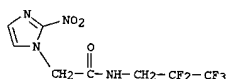


REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L11 ANSWER 8 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:644457 CAPLUS
DOCUMENT NUMBER: 137:29877
TITLE: Pharmacokinetics of EF5
[2-(2-nitro-1-H-imidazol-1-yl)-
N-(2,2,3,3,3-pentafluoropropyl) acetamide] in
human
patients; implications for hypoxia measurements in
vivo by 2-nitroimidazoles
AUTHOR(S): Koch, C. J.; Hahn, S. M.; Rockwell, K., Jr.;
Covey, J.
CORPORATE SOURCE: M.; McKenna, W. G.; Evans, S. M.
University of Pennsylvania School of Medicine,
Radiation Oncology, Philadelphia, PA, 19104-6072,
USA
SOURCE: Cancer Chemotherapy and Pharmacology (2001),
48 (3),
177-187
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objectives: Pharmacokinetic studies were performed on the 1st 28
patients
enrolled in a phase I trial to det. the ability of EF5
[2-(2-nitro-1-H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)
acetamide]
to detect hypoxia in human tumors in the absence of patient toxicity.
Methods: EF5 was made in purified form and formulated for i.v.
injection
by the National Cancer Institute. After obtaining consent from the
patients, EF5 was administered and blood samples were drawn at various
times over approx. 48 h. For most patients it was possible to collect
total urine at approx. 8-h intervals. EF5 in plasma and urine was
analyzed by high-performance liq. chromatog. Results: EF5's blood
plasma
concn. followed a simple exponential decay following infusion. The
plasma
half-life was 11.7 h and was not affected by drug dose (9 to 28
mg/kg),
fractional urine recovery, patient wt., or gender. Abs. plasma values
suggested even biodistribution of the drug throughout the soft tissue
with
a vol. of distribution equal to 0.56 l/kg. Despite the relatively
high
lipid partition coeff. (logP=0.6), EF5 was excreted primarily
(.ltoreq.
70%) via kidney clearance. No drug metabolites (e.g. retaining the
2-nitroimidazole chromophore) were detected in either plasma or
urine. No
toxicity was found at drug doses adequate to detect tumor hypoxia.
Conclusions: Currently held paradigms of 2-nitroimidazole metab. (e.g.
clearance rate and toxicity as affected by octanol/water partition
coeff.)
are discussed. The results reported herein suggest that EF5 is biol.
stable with predictable pharmacokinetics. EF5's consistent half-life
and

L11 ANSWER 8 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
clearance properties will allow quant. anal. of EF5 binding relative
to
tissue oxygen levels.
IT 152721-37-4, EF5
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological
study); USES (Uses)
(pharmacokinetics of EF5 in human cancer patients)
RN 152721-37-4 CAPLUS
CN 1H-imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-
(9CI)
(CA INDEX NAME)



REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

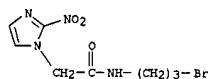
L11 ANSWER 9 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:468223 CAPLUS
DOCUMENT NUMBER: 135:58183
TITLE: Nitroaromatic compounds for the detection of
hypoxia
INVENTOR(S): Koch, Cameron J.; Kachur, Alexander V.; Evans,
Sydney
M.; Shive, Chyng-yann; Baird, Ian R.; Skov,
Kirsten
A.; Dolbier, Jr William R.; Li, An-rong; James,
Brian
R.
PATENT ASSIGNEE(S): Trustees of the University of Pennsylvania, USA
SOURCE: U.S., 17 pp., Cont.-in-part of U.S. 5,843,404.
CODEN: USKXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

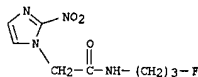
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6252087	B1	20010626	US 1998-123300	19980728
US 5540908	A	19960730	US 1994-286065	19940804
US 5843404	A	19981201	US 1996-598752	19960208
PRIORITY APPLN. INFO.:			US 1992-978918	B2 19921119
			US 1994-286065	A3 19940804
			US 1996-598752	A2 19960208

OTHER SOURCE(S): MARPAT 135:58183
AB Nitroarom. compds. and immunogenic conjugates comprising a novel
nitroarom. compd. and a carrier protein are disclosed. The invention
further presents monoclonal antibodies highly specific for the claimed
nitroarom. compds., the compds.' protein conjugates, the compds.'
reductive byproducts, and adducts formed between the compds. and
mammalian
hypoxic cell tissue proteins. The invention is further directed to
methods for detecting tissue hypoxia using immunohistol. techniques,
non-invasive nuclear medicinal methods, or NMR. Diagnostic kits
useful in
practicing the methods of claimed invention are also provided.
IT 252736-27-9DP, compds. contg. 252736-28-0P
345658-88-0P 345658-89-1P 345658-90-4P
345658-91-5P 345658-92-6P 345658-93-7P
345658-94-8P
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified);
SPN (Synthetic preparation); THU (Therapeutic use); ANST (Analytical
study);
BIOL (Biological study); PREP (Preparation); USES (Uses)
(nitroarom. compds. for detection of hypoxia)
RN 252736-27-9 CAPLUS
CN 1H-imidazole-1-acetamide, N-(3-bromopropyl)-2-nitro- (9CI) (CA INDEX
NAME)

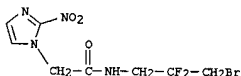
L11 ANSWER 9 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



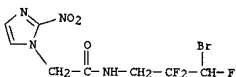
RN 252736-28-0 CAPLUS
CN 1H-imidazole-1-acetamide, N-(3-fluoropropyl)-2-nitro- (9CI) (CA
INDEX NAME)



RN 345658-88-0 CAPLUS
CN 1H-imidazole-1-acetamide, N-(3-bromo-2,2-difluoropropyl)-2-nitro- (9CI)
(CA INDEX NAME)

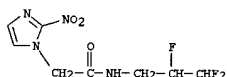


RN 345658-89-1 CAPLUS
CN 1H-imidazole-1-acetamide, N-(3-bromo-2,2,3-trifluoropropyl)-2-nitro- (9CI)
(CA INDEX NAME)

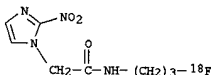


RN 345658-90-4 CAPLUS
CN 1H-imidazole-1-acetamide, N-(2-bromo-3-fluoropropyl)-2-nitro- (9CI)
(CA INDEX NAME)

L11 ANSWER 9 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

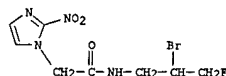


IT 252736-29-1P
RL: BUU (Biological use, unclassified); SPN (Synthetic preparation);
THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
(Uses)
(nitroarom. compds. for detection of hypoxia)
RN 252736-29-1 CAPLUS
CN 1H-imidazole-1-acetamide, N-[3-(fluoro-18F)propyl]-2-nitro- (9CI)
(CA INDEX NAME)

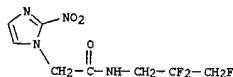


REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

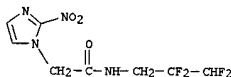
L11 ANSWER 9 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



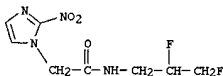
RN 345658-91-5 CAPLUS
CN 1H-imidazole-1-acetamide, 2-nitro-N-(2,2,3-trifluoropropyl)- (9CI)
(CA INDEX NAME)



RN 345658-92-6 CAPLUS
CN 1H-imidazole-1-acetamide, 2-nitro-N-(2,2,3,3-tetrafluoropropyl)- (9CI)
(CA INDEX NAME)



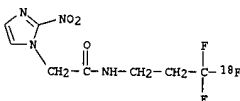
RN 345658-93-7 CAPLUS
CN 1H-imidazole-1-acetamide, N-(2,3-difluoropropyl)-2-nitro- (9CI) (CA
INDEX NAME)



RN 345658-94-8 CAPLUS
CN 1H-imidazole-1-acetamide, 2-nitro-N-(2,3,3-trifluoropropyl)- (9CI)
(CA INDEX NAME)

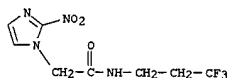
L11 ANSWER 10 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:322270 CAPLUS
DOCUMENT NUMBER: 135:76826
TITLE: Synthesis of [18F]-labeled EF3
[2-(2-nitroimidazol-1-yl)-N-(3,3,3-trifluoropropyl)acetamide], a marker
for PET detection of hypoxia
AUTHOR(S): Josse, Olivier; Labar, Daniel; Georges, Benoit;
Gregoire, Vincent; Marchand-Brynaert, Jacqueline
CORPORATE SOURCE: Unite de Chimie Organique et Medicinale,
Universite catholique de Louvain, Louvain-la-Neuve, B-1348,
Belg.
SOURCE: Bioorganic & Medicinal Chemistry (2001), 9(3),
665-675
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 135:76826
AB [18F]-2-(2-Nitroimidazol-1-yl)-N-(3,3,3-trifluoropropyl)acetamide
([18F]-EF3) has been prepd. in 65% chem. yield and 5% radiochem.
yield by coupling 2,3,5,6-tetrafluorophenyl 2-(2-nitroimidazol-1-yl)acetate
with [18F]-3,3,3-trifluoropropylamine. This original radiolabeled key
synthon was obtained in 40% overall chem. yield by oxidative [18F]-
fluorodesulfurization of Et N-phthalimido-3-aminopropanedithioate,
followed by deprotection with hydrazine of the resulting
[18F]-N-phthalimido-3,3,3-trifluoropropylamine. The process was
performed within 90 min, from the [18F]-HF prodn. in the cyclotron to the
purifn. of the final target.
IT 347190-26-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 347190-26-5 CAPLUS
CN 1H-imidazole-1-acetamide,
N-[3,3,3-difluoro-3-(fluoro-18F)propyl]-2-nitro- (9CI)
(CA INDEX NAME)

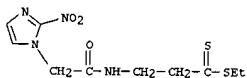


IT 180208-73-5P 347190-22-1P 347190-23-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of [18F]-labeled EF3 [2-(2-nitroimidazol-1-yl)-N-(3,3,3-

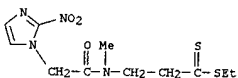
L11 ANSWER 10 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
trifluoropropyl]acetamide])
RN 180208-73-5 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoropropyl)- (9CI)
(CA INDEX NAME)



RN 347190-22-1 CAPLUS
CN Propane(dithioic) acid, 3-[[[(2-nitro-1H-imidazol-1-yl)acetyl]amino]-, ethyl ester (9CI) (CA INDEX NAME)

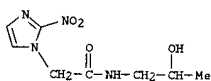


RN 347190-23-2 CAPLUS
CN Propane(dithioic) acid, 3-[[[(2-nitro-1H-imidazol-1-yl)acetyl]amino]-, ethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L11 ANSWER 11 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
RL: BAC (Biological activity or effector, except adverse); BSU
(Biological study, unclassified); FRP (Properties); SPN (Synthetic preparation);
THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
(Uses)
(nitroimidazoleacetamides as antimetastatic hypoxic cell
radiosensitizers)
RN 220914-96-5 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2-hydroxypropyl)-2-nitro- (9CI) (CA
INDEX NAME)

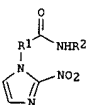


REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE
FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L11 ANSWER 11 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:162888 CAPLUS
DOCUMENT NUMBER: 134:363402
TITLE: New antimetastatic hypoxic cell radiosensitizers: design, synthesis, and biological activities of 2-nitroimidazole-acetamide, TX-1877, and its analogues
AUTHOR(S): Kasai, S.; Nagasawa, H.; Yamashita, M.; Masui, M.; Kuwasaka, H.; Oshodani, T.; Uto, Y.; Inomata, T.; Oka, S.; Inayama, S.; Hori, H.
CORPORATE SOURCE: Faculty of Engineering, Department of Biological Science and Technology, The University of Tokushima, Tokushima, 770-8506, Japan
SOURCE: Bioorganic & Medicinal Chemistry (2001), 9(2), 453-464
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We designed, based on the MO (MO) calcul., synthesized, and evaluated the biol. activities of the new antimetastatic hypoxic cell radiosensitizer, 2-nitroimidazole-acetamide, TX-1877, and its analogs. Each analog has an electron-affinic imidazole group, an acetamide group and a certain hydrophilic group to control its biol. effect, toxicity, and pharmacokinetics. In vitro radiosensitization assay, most TX-1877 analogs, which have an electron affinity (EA) of more than 0.9 eV and partition coeff. (P) of more than 0.021, showed satisfactory enhancement ratios (ER > 1.60) at doses of 1 mM. On the other hand, imidazole analogs, such as TX-1908 (EA=0.67 eV), TX-1910 (EA=-0.34 eV) and TX-1931 (EA=-0.37 eV), which have low electron affinities, had an ER of 1.31 or less. TX-1877 and KIN-806 effectively inhibited tumor regrowth when administered with irradiation in vivo at a dose of 0.4 mg/g. Tumor lung metastasis was inhibited by treatment with either TX-1877 or KIN-806 without irradiation at a dose of 0.4 mg/g. TX-1877 reduced markedly the mean no. of metastatic lung nodules in comparison with KIN-806. Moreover, TX-1877 and KIN-806 enhanced macrophage and helper T lymphocyte infiltration for 3 wk after drug treatment. TX-1877 shows a high EA value and has the C2 of HOMO localizing on N-methylamide and the C2 of LUMO localizing on 2-nitroimidazole group. The MO data might be useful for designing a bifunctional hypoxic cell radiosensitizer. TX-1877 and its analogs are potential antimetastatic hypoxic cell radiosensitizers, which would improve the efficiency of radiotherapy and quality of life in cancer treatment.
IT 220914-96-5P, TX 1909

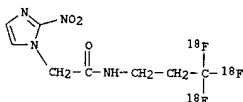
L11 ANSWER 12 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:137166 CAPLUS
DOCUMENT NUMBER: 134:178558
TITLE: Preparation of perfluorinated [18F]-radiolabeled nitroimidazole derivatives for cellular hypoxia detection.
INVENTOR(S): Marchand, Jacqueline; Gregoire, Vincent
PATENT ASSIGNEE(S): Universite Catholique de Louvain, Belg.
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012575	A1	20010222	WO 2000-EP4632	20000522
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1202945	A1	20020508	EP 2000-936775	20000522
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
PRIORITY APPLN. INFO.:				
			EP 1999-070172	A 19990811
			WO 2000-EP4632	W 20000522
OTHER SOURCE(S):			MARPAT 134:178558	
GI				

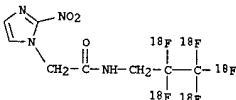


AB Title compds. (I; R1 = CH2; R2 = CHXCK2CV3; X = H, halo; Y = F), were prepd. for cellular hypoxia detection (no data). I preferably have an

L11 ANSWER 12 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
incorporation of [18F] atoms sufficient to give specific
radioactivity of
1-30 Ci/mmol, preferably between 1-20 Ci/mmol, and most preferably
1-10
Ci/mmol. Tissue hypoxia in a patient is diagnosed by introducing I
into a
patient, imaging tissue hypoxia in said patient, and quantifying
tissue
hypoxia. Thus, [18F]-3,3,3-trifluoropropylamine was distd. and
condensed
into a 0.degree. soln. of 2,3,5,6-tetrafluorophenyl
2-(2-nitroimidazol-1-
yl)acetate followed by stirring for 30 min. at 20.degree. to give 63%
[18F]-2-(2-nitro-1H-imidazol-1-yl)-N-(3,3,3-trifluoropropyl)acetamide.
IT 326590-99-2P 326591-00-8P
RL: BAC (Biological activity or effector, except adverse); BSU
(Biological
study, unclassified); SPN (Synthetic preparation); THU (Therapeutic
use);
BIOL (Biological study); PREP (Preparation); USES (Uses)
(prep. of perfluorinated [18F]-radiolabeled nitroimidazole
derivs. for
cellular hypoxia detection)
RN 326590-99-2 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-[3,3,3-tri(fluoro-18F)propyl]-
(9CI)
(CA INDEX NAME)



RN 326591-00-8 CAPLUS
CN 1H-Imidazole-1-acetamide,
2-nitro-N-[2,2,3,3,3-penta(fluoro-18F)propyl]-
(9CI) (CA INDEX NAME)

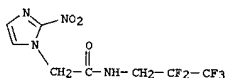


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR
THIS

L11 ANSWER 13 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:113367 CAPLUS
DOCUMENT NUMBER: 135:134082
TITLE: Hypoxia in human intraperitoneal and extremity
sarcomas
AUTHOR(S): Evans, S. M.; Hahn, S. M.; Magarelli, D. P.;
Zhang, P.
J.; Jenkins, W. T.; Fraker, D. L.; Hsi, R. A.;
McKenna, W. G.; Koch, C. J.
CORPORATE SOURCE: From the School of Veterinary Medicine,
University of
Pennsylvania, Philadelphia, PA, USA
SOURCE: International Journal of Radiation Oncology,
Biology,
Physics (2001), 49(2), 587-596
CODEN: IORPD3; ISSN: 0360-3016
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The presence of hypoxia, measured by needle electrodes, was shown to
be
assocd. with poor patient outcome in several human tumor types,
including
soft tissue sarcomas. The present report emphasizes the evaluation
of
hypoxia in soft tissue sarcomas based upon the binding of the
2-nitroimidazole drug EF5 (2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-
pentafluoropropyl) acetamide). EF5 has previously been shown to be
predictive of radiation response in animal tumors and in in vitro
studies.
The authors have also previously reported studies of EF5 binding in
human
squamous cell tumors. Using fluorescent immunohistochem.
techniques, the
authors provide data on the presence and distribution of EF5
binding, as a
surrogate for hypoxia, in human spindle cell tumors. Patients with
spindle cell tumors who were scheduled for tumor surgery were asked
to
participate in the phase I trial of EF5. Approx. 48 h
preoperatively, EF5
was administered i.v. at doses between 9 and 21 mg/kg. Binding in
frozen
sections of biopsied tissues was detd. using monoclonal antibodies
labeled
with the green-excited, orange-emitting fluorescent dye, Cy3.
Calibration
studies were performed in vitro by incubating fresh tumor tissue
cubes
obtained from each patient with EF3 (an analog of EF5) under hypoxic
conditions ("ref. binding"). The goal of these calibration studies
was to
quantify the maximal binding levels possible in individual patient's
tissues. The relationship between binding (in situ based on EF5
binding)
and ref. binding (in vitro based on EF3 binding) was detd. 8
Patients

L11 ANSWER 12 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L11 ANSWER 13 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
were studied; 3 of these patients had gastrointestinal stromal tumors
(GIST). The incubation of tumor tissue cubes in EF3 under hypoxic
conditions demonstrated that all tumors bound drug to a similar
extent.
Ref. binding showed a 3.2-fold variation in median fluorescence
(113-356)
on an abs. fluorescence scale, calibrated by a Cy3 dye std. In situ
binding in the brightest tumor section varied by a factor of 25.4
between
the lowest and highest binding tumor (7.5-190.2). Heterogeneity of
highest binding was greater between tumors than within individual
tumors.
A correspondence between EF5 binding and Eppendorf needle electrode
studies was seen in the 5 patients with non-GISTs. Inter- and
intratumoral heterogeneity of EF5 binding in spindle cell tumors was
documented. Patterns of binding consistent with diffusion limited
hypoxia
are present in human spindle cell neoplasms.
IT 152721-37-4, EF5
RL: ARG (Analytical reagent use); BUU (Biological use, unclassified);
ANST (Analytical study); BIOL (Biological study); USES (Uses)
(hypoxia anal. in sarcomas by immunohistochem. using EF5)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-
(9CI)
(CA INDEX NAME)

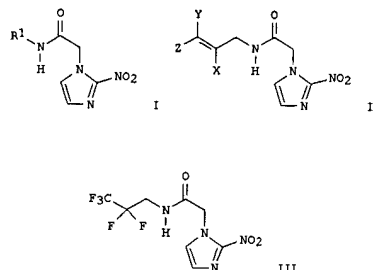


REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR
THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L11 ANSWER 14 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:78365 CAPLUS
DOCUMENT NUMBER: 134:147601
TITLE: Preparation of fluorinated nitroimidazole
compounds and their labeled counterparts for the detection
of hypoxia
INVENTOR(S): Dolbier, William R.; Li, An-Rong; Koch, Cameron
J.; Kachur, Alexander V.
PATENT ASSIGNEE(S): The Trustees of the University of Pennsylvania,
USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

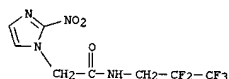
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007414	A1	20010201	WO 2000-US40437	20000720
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH,				
CN,	CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,			
HR,	HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,			
LT,	LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,			
RU,	SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,			
VN,	YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
CY,	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH,			
BJ,	DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF,			
EP 1202973	CF, CG, CI, CH, GA, GN, GW, ML, MR, NE, SN, TD, TG			
PT,	A1 20020508 EP 2000-960168 20000720			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC,			
	IE, SI, LT, LV, FI, RO, MK, CY, AL			
PRIORITY APPLN. INFO.:	US 1999-144747P P 19990721			
GI	WO 2000-US40437 W 20000720			

L11 ANSWER 14 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

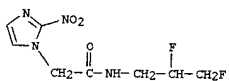


AB Methods for prep. novel fluorinated nitroimidazoles I [R1 = CH2CHFCH2F, CH2CHFCH2F3, CH2CH2CH2F, CH2CF2CHF2, and CH2CF2CF3], their 18F-labeled counterparts [at least one F is 18F], along with their corresponding intermediates II [X, Y, and Z are independently H or F] are disclosed. Thus, III (EF5) was prepd. by fluorination of the allyl precursor 2-(2-nitro-1H-imidazol-1-yl)-N-(2,3,3-trifluoroallyl)acetamide (II; X = Y = Z = F). The title compds. are disclosed as agents for non-invasive imaging techniques, such as PET, for detecting tissue hypoxia and demonstrated in PET imaging of a tumor-bearing rat treated with [18F]-labeled EF5. Diagnostic kits useful in practicing the methods of claimed invention are also provided.
IT 152721-37-4P 322637-51-4P 322637-52-5P
322637-53-6P 322637-54-7P 322637-55-8P
322637-56-9P
RI: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (prepn. of fluorinated nitroimidazoles and their labeled counterparts as medical imaging agents for the detection of hypoxia)
RN 152721-37-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI) (CA INDEX NAME)

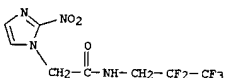
L11 ANSWER 14 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



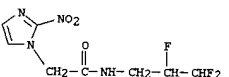
RN 322637-51-4 CAPLUS
CN 1H-imidazole-1-acetamide, N-(2,3-difluoropropyl)-2-nitro-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



RN 322637-52-5 CAPLUS
CN 1H-imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)

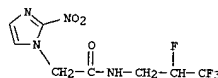


RN 322637-53-6 CAPLUS
CN 1H-imidazole-1-acetamide, 2-nitro-N-(2,3,3-trifluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)

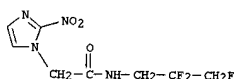


RN 322637-54-7 CAPLUS
CN 1H-imidazole-1-acetamide, 2-nitro-N-(2,3,3-tetrafluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)

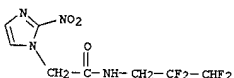
L11 ANSWER 14 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



RN 322637-55-8 CAPLUS
CN 1H-imidazole-1-acetamide, 2-nitro-N-(2,2,3-trifluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



RN 322637-56-9 CAPLUS
CN 1H-imidazole-1-acetamide, 2-nitro-N-(2,2,3,3-tetrafluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)

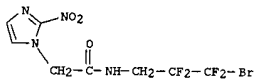


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

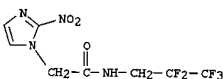
L11 ANSWER 15 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 2000:806871 CAPLUS
 DOCUMENT NUMBER: 134:207753
 TITLE: [18F]-EF5, a marker for PET detection of hypoxia: synthesis of precursor and a new fluorination procedure
 AUTHOR(S): Dolbier, W. R.; Li, A.-R.; Koch, C. J.; Shue, C.-Y.;
 CORPORATE SOURCE: Kachur, A. V.
 Department of Chemistry, University of Florida,
 Gainesville, FL, 32611, USA
 SOURCE: Applied Radiation and Isotopes (2000), Volume
 Date 2001, 54(1), 73-80
 CODEN: ARISEF; ISSN: 0969-8043
 PUBLISHER: Elsevier Science Ltd.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 134:207753
 AB There is a great deal of clin. and exptl. interest in detg. tissue hypoxia using non-invasive imaging methods. The authors have previously developed EF5, 2-(2-nitro-1[H]-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide, with both invasive and non-invasive hypoxia detection in mind. EF5 and other 2-nitroimidazoles are used to detect hypoxia, because the rate of their bioreductive metab. is inversely dependent on oxygen partial pressure. Such metab. leads to the formation of covalent adducts within the metabolizing cells. Previously, the authors have described the invasive detection of these adducts by highly specific monoclonal antibodies after tissue biopsy. In this work, the authors synthesized 18F-labeled EF5, [18F]-2-(2-nitro-1[H]-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide, in greater than 10% yield by direct fluorination of the newly synthesized precursor 2-(2-nitro-1[H]-imidazol-1-yl)-N-(2,2,3,3-trifluoroallyl)acetamide by [18F]-F2 in trifluoroacetic acid. The objective was to optimize the electrophilic fluorination of the fluorinated alkene bond with fluorine gas, a new method of 18F-labeling of polyfluorinated mols. Previous EF5 to biodistribution studies in mice have demonstrated uniform access of all tissues with bioelimination dominated by renal excretion. When [18F]-EF5 was injected into a rat followed by urine collection and anal., the authors found no detectable metab. to other radioactive compds. Thus, [18F]-EF5 should be well suited for use as a non-invasive hypoxia marker with detection using positron emission tomog. (PET).
 IT 328386-75-0P

L11 ANSWER 15 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS
 FORMAT RECORD. ALL CITATIONS AVAILABLE IN THE RE

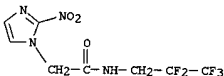
L11 ANSWER 15 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
 RACT (Reactant or reagent)
 (using electrophilic fluorination in acidic medium to prep.
 [18F]-EF5, marker for PET detection of hypoxia)
 RN 328386-75-0 CAPLUS
 CN 1H-imidazole-1-acetamide,
 N-(3-bromo-2,2,3,3-tetrafluoropropyl)-2-nitro-
 (9CI) (CA INDEX NAME)



IT 152721-37-4P, EF5
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (using electrophilic fluorination in acidic medium to prep.
 [18F]-EF5, marker for PET detection of hypoxia)
 RN 152721-37-4 CAPLUS
 CN 1H-imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-
 (9CI) (CA INDEX NAME)

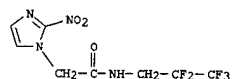


IT 322637-52-5P
 RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (using electrophilic fluorination in acidic medium to prep.
 [18F]-EF5, marker for PET detection of hypoxia)
 RN 322637-52-5 CAPLUS
 CN 1H-imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-, labeled with fluorine-18 (9CI) (CA INDEX NAME)



L11 ANSWER 16 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 2000:248505 CAPLUS
 DOCUMENT NUMBER: 133:29066
 TITLE: Detection of hypoxia in human squamous cell carcinoma
 AUTHOR(S): by EF5 binding
 Evans, Sydney M.; Hahn, Stephen; Pook, Deirdre R.;
 Jenkins, W. Timothy; Chalian, Ara A.; Zhang, Paul;
 Stevens, Craig; Weber, Randall; Weinstein,
 Gregory; Benjamin, Ivor; Mirza, Natasha; Morgan, Mark;
 Rubin, Steven; McKenna, W. Gillies; Lord, Edith M.; Koch, Cameron J.
 CORPORATE SOURCE: Schools of Veterinary Medicine, University of
 Pennsylvania, Philadelphia, PA, 19104, USA
 SOURCE: Cancer Research (2000), 60(7), 2018-2024
 CODEN: CNREA8; ISSN: 0008-5472
 PUBLISHER: American Association for Cancer Research
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Localization and quantitation of 2-nitroimidazole drug binding in low pO2 tumors is a technique that can allow the assessment of hypoxia as a predictive assay. EF5 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl) acetamide] is such a drug, and it has been shown to be predictive of radiation response in rodent tumors. Using fluorescence immunohistochem. techniques, data on the presence, distribution, and levels of EF5 binding as a surrogate for hypoxia in human head and neck and uterine cervix squamous-cell cancers (SCCs) are provided. Six patients with SCC were studied. Four patients had head and neck tumors, and two had uterine cervix cancers. The incubation of fresh tissue cubes in EF5 under hypoxic conditions ("ref. binding") demonstrated that all tumors were capable of binding drug, and that this binding varied by a factor of 2.9-fold (174.5-516.1) on an abs. fluorescence scale. In the five patients treated at the lowest drug doses (9 mg/kg), in situ binding was quantifiable. For all six patients, the max. rate of in situ binding varied by a factor of 6.7 between the lowest and highest binding tumor (24.8-160.3) on an abs. fluorescence scale. In tumors with high binding regions, intratumoral heterogeneity was large, extending from minimal fluorescence (<1%) up to 88.6% of ref. binding. In tumors with minimal binding, there was little intratumoral heterogeneity. These studies demonstrate substantial heterogeneity of in situ binding between and within individual squamous-cell tumors.
 IT 152721-37-4, EF5
 RL: BFR (Biological process); BSU (Biological study, unclassified);
 BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process);

L11 ANSWER 16 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 USES (Uses)
 (detection of hypoxia in human squamous-cell carcinoma by EF5
 binding)
 RN 152721-37-4 CAPLUS
 CN 1H-imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-
 (9CI)
 (CA INDEX NAME)

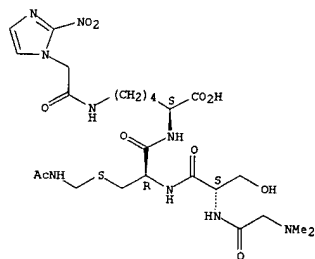


REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE
 FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
 FORMAT

L11 ANSWER 17 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 2000:243597 CAPLUS
 DOCUMENT NUMBER: 133:55392
 TITLE: Targeting Hypoxia in Tumors Using
 2-Nitroimidazoles with Peptidic Chelators for Technetium-99m:
 Effect of Lipophilicity
 AUTHOR(S): Zhang, Xiuguor; Su, Zi-Fen; Ballinger, James R.;
 Rauth, A. M.; Pollak, Alfred; Thornback, John R.
 CORPORATE SOURCE: Division of Experimental Therapeutics, Ontario
 Cancer Institute, Toronto, ON, M5G 2M9, Can.
 SOURCE: Bioconjugate Chemistry (2000), 11(3), 401-407
 CODEN: BCCHE; ISSN: 1043-1802
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Tumor hypoxia is an important prognostic factor for response to
 therapy. Radiolabeled 2-nitroimidazoles have been used for imaging hypoxia,
 and the octanol/water partition coeff. (P) of these compds. appears to play a
 crucial role in their suitability for imaging. A series of 11
 2-nitroimidazoles coupled to peptidic chelators for 99mTc with
 divergent P was developed and evaluated in an in vitro system. Two classes of N3S
 chelators were used: dialkyl-Gly-Ser-Cys-linker-2-nitroimidazole
 (Class I) and dialkyl-Gly-Lys(2-nitroimidazole)-Cys (Class II). The chelators
 were prepd. by automated solid-phase peptide synthesis. Xanthine oxidase
 was able to reduce the 2-nitroimidazole moiety on the ligands, but the
 rate of redn. varied 5-fold among the different chelators. The chelators
 were labeled by transchelation from [99mTc]gluconate at temps. between 22
 and 100 degree.C. The reaction mixts. were analyzed by HPLC and their P
 values detd. The accumulation of each complex in suspension cultures
 of Chinese hamster ovary cells incubated under aerobic or extremely
 hypoxic conditions was detd. Radiochem. yields ranged from 5 to 80% for the
 11 compds. HPLC showed that some of the compds. formed two complexes with
 99mTc, possibly syn and anti conformations with respect to the Tc:O
 bond.
 In general, the Class I chelators labeled more readily than the class
 II chelators. The P values of the 99mTc complexes varied from 0.0002 to
 5 and were generally in accordance with predictions based on structure.
 There were also differences in P as a function of pH; the free acids
 had a

L11 ANSWER 17 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 lower P at pH 7.4 than at pH 2.0 due to ionization, whereas the
 amides did not show this effect. Accumulation levels in aerobic cells were
 related to P but varied over a narrow range. Four of the 11 compds. showed
 selective accumulation in hypoxic cells. The peptidic class of
 2-nitroimidazoles, with flexible design and convenient solid-phase
 synthesis, deserves further study as agents for imaging hypoxia in
 tumors.
 IT 248249-24-3DP, 99mTc-labeled 276878-98-9DP,
 99mTc-labeled 276879-99-0DP, 99mTc-labeled 276879-00-6DP
 , 99mTc-labeled 276879-01-7DP, 99mTc-labeled
 276879-02-8P 276879-03-9DP, 99mTc-labeled
 276879-04-0DP, 99mTc-labeled 276879-05-1DP,
 99mTc-labeled
 RL: BPR (Biological process); BSU (Biological study, unclassified);
 PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study);
 PREP (Preparation); PROC (Process)
 (targeting hypoxia in tumors using 2-nitroimidazoles with peptidic
 chelators for technetium-99m)
 RN 248249-24-3 CAPLUS
 CN L-lysine,
 N,N-dimethylglycyl-L-seryl-S-[(acetylamino)methyl]-L-cysteinyl-
 N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX NAME)

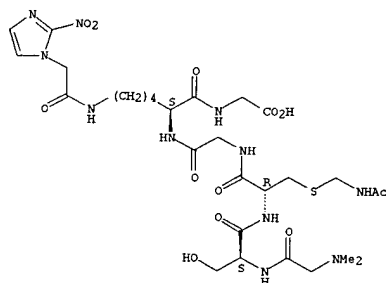
Absolute stereochemistry.



RN 276878-98-9 CAPLUS
 CN Glycine, N,N-dimethylglycyl-L-seryl-S-[(acetylamino)methyl]-L-
 cysteinylglycyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-lysyl- (9CI)
 (CA INDEX NAME)

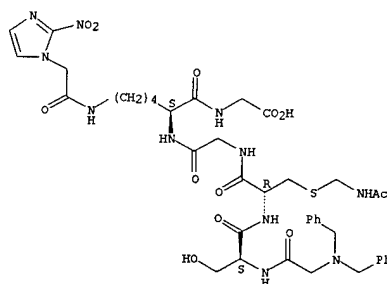
Absolute stereochemistry.

L11 ANSWER 17 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



RN 276878-99-0 CAPLUS
 CN Glycine,
 N,N-bis(phenylmethyl)glycyl-L-seryl-S-[(acetylamino)methyl]-L-
 cysteinylglycyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-lysyl- (9CI)
 (CA INDEX NAME)

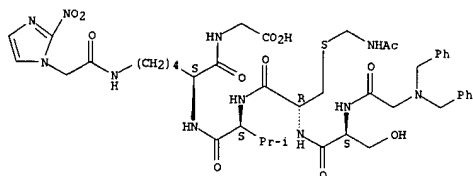
Absolute stereochemistry.



RN 276879-00-6 CAPLUS
 CN Glycine,
 N,N-bis(phenylmethyl)glycyl-L-seryl-S-[(acetylamino)methyl]-L-

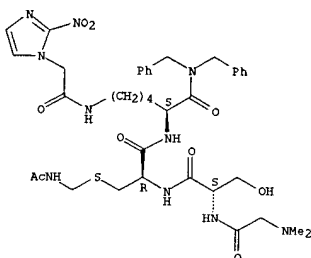
L11 ANSWER 17 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 cysteinyl-L-valyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-lysyl-
 (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 276879-01-7 CAPLUS
 CN L-Lysinamide, N,N-dimethylglycyl-L-seryl-S-[(acetylamino)methyl]-L-cysteinyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-N,N-bis(phenylmethyl)- (9CI) (CA INDEX NAME)

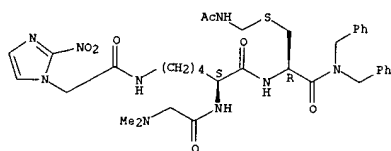
Absolute stereochemistry.



RN 276879-02-8 CAPLUS
 CN L-Cysteine,
 N,N-dimethylglycyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-lysyl-S-[(acetylamino)methyl]- (9CI) (CA INDEX NAME)

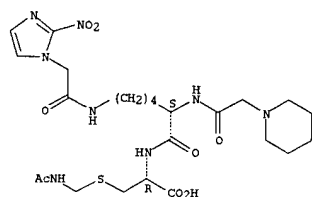
Absolute stereochemistry.

L11 ANSWER 17 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



RN 276879-05-1 CAPLUS
 CN L-Cysteine,
 N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-N2-(1-piperidinylacetyl)-L-lysyl-S-[(acetylamino)methyl]- (9CI) (CA INDEX NAME)

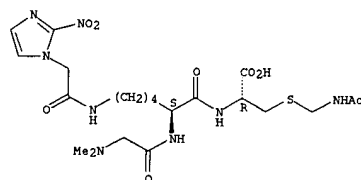
Absolute stereochemistry.



IT 276879-06-2DP, 99mTc-labeled 276879-07-3DP,
 99mTc-labeled
 RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
 (targeting hypoxia in tumors using 2-nitroimidazoles with peptidic
 chelators for technetium-99m)
 RN 276879-06-2 CAPLUS
 CN L-Cysteine, N,N-bis(phenylmethyl)glycyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-lysyl-S-[(acetylamino)methyl]- (9CI) (CA INDEX NAME)

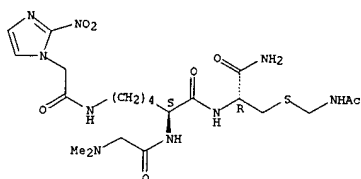
Absolute stereochemistry.

L11 ANSWER 17 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



RN 276879-03-9 CAPLUS
 CN L-Cysteinamide,
 N,N-dimethylglycyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-lysyl-S-[(acetylamino)methyl]- (9CI) (CA INDEX NAME)

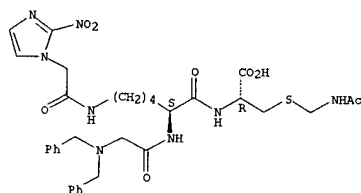
Absolute stereochemistry.



RN 276879-04-0 CAPLUS
 CN L-Cysteinamide,
 N,N-dimethylglycyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-lysyl-S-[(acetylamino)methyl]-N,N-bis(phenylmethyl)- (9CI) (CA INDEX NAME)

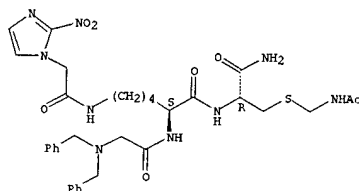
Absolute stereochemistry.

L11 ANSWER 17 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



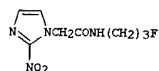
RN 276879-07-3 CAPLUS
 CN L-Cysteinamide,
 N,N-bis(phenylmethyl)glycyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-lysyl-S-[(acetylamino)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

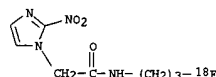
L11 ANSWER 18 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 2000:135450 CAPLUS
 DOCUMENT NUMBER: 133:55383
 TITLE: Noninvasive detection of tumor hypoxia using the 2-nitroimidazole [18F]EF1
 AUTHOR(S): Evans, Sydney M.; Kachur, Alexander V.; Shiu, Chyng-Yann; Hustink, Roland; Jenkins, W. Timothy; Shive, Grace G.; Karp, Joel S.; Alavi, Abbas;
 Lord, Edith M.; Dolbier, William R., Jr.; Koch, Cameron J.
 CORPORATE SOURCE: Schools of Medicine and Veterinary Medicine, University of Pennsylvania, Philadelphia, PA, USA
 SOURCE: Journal of Nuclear Medicine (2000), 41(2), 327-336
 CODEN: JNMEAQ; ISSN: 0161-5505
 PUBLISHER: Society of Nuclear Medicine, Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The noninvasive assessment of tumor hypoxia in vivo is under active investigation because hypoxia has been shown to be an important prognostic factor for therapy resistance. Various nuclear medicine imaging modalities are being used, including PET imaging of 18F-contg. compds. In this study, we report the development of 18F-labeled EF1 for noninvasive imaging of hypoxia. EF1 is a 3-monofluoro analog of the well-characterized hypoxia marker EF5, 2(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide, which has been used to detect hypoxia in tumor and nontumor systems using immunohistochem. methods. We have studied 2 rat tumor types: the hypoxic Morris 7777 (Q7) hepatoma and the oxix 9LF glioma tumor, each grown in s.c. sites. PET studies were performed using a pharmacol. dose of nonradioactive carrier in addn. to [18F]EF1 to optimize and assess drug biodistribution. After PET imaging of the tumor-bearing rats, tissues were obtained for .gamma.-counting of the 18F in various tissues and immunohistochem. detection of intracellular drug adducts in tumors. In one pair of tumors, Eppendorf needle electrode studies were performed. [18F]EF1 was excreted dominantly through the urinary tract. The tumor-to-muscle (T/M) ratio of [18F]EF1 in the Q7 tumors was 2.7 and 2.4 based on PET studies and 2.1, 2.5, and 3.0 based on .gamma.-counting of the tissues (n = 3). In contrast, the T/M ratio of [18F]EF1 in the 9LF glioma tumor was 0.8 and 0.5 based on PET studies and 1.0, 1.2, and 1.4 based on .gamma.-counting of the tissues (n = 3). Immunohistochem. anal. of drug adducts for the two tumor types agreed with



I

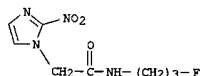
AB We report on the prepn. of a hypoxia marker 2-(2-nitroimidazol-1-[H]-yl)-N-(3-fluoropropyl)acetamide (EF1, I) and its 18F analog. Two methods for the prepn. of 3-fluoropropylamine, the EF1 side chain, are described. [18F]-EF1 was prepd. with a radiochem. yield of 24 by nucleophilic substitution of bromine in 2-(2-nitroimidazol-1-[H]-yl)-N-(3-bromopropyl)acetamide (EB1) by carrier-added 18F in DMSO at 120.degree.. Our results demonstrate the prepn. of clin. relevant amts. of [18F]-EF1 for use as a non-invasive hypoxia marker with detection using positron emission tomog.
 IT 252736-27-9P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (prepn. and reaction with fluoride)
 RN 252736-27-9 CAPLUS
 CN 1H-Imidazole-1-acetamide, N-(3-bromopropyl)-2-nitro- (9CI) (CA INDEX NAME)

L11 ANSWER 18 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 the radioactivity anal. In the Q7 tumor, substantial heterogeneous binding was obsd. throughout the tumor, whereas in the 9LF tumor minimal binding was found. [18F]EF1 is an excellent radiotracer for noninvasive imaging of tumor hypoxia.
 IT 252736-29-1
 RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses) (detection of tumor hypoxia using 2-nitroimidazole [18F]EF1)
 RN 252736-29-1 CAPLUS
 CN 1H-Imidazole-1-acetamide, N-[3-(fluoro-18F)propyl]-2-nitro- (9CI) (CA INDEX NAME)

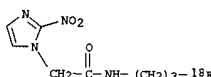


REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L11 ANSWER 19 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 IT 252736-28-0P 252736-29-1P
 RL: SPN (Synthetic preparation); PREP (Preparation) (prepn. of)
 RN 252736-28-0 CAPLUS
 CN 1H-Imidazole-1-acetamide, N-(3-fluoropropyl)-2-nitro- (9CI) (CA INDEX NAME)

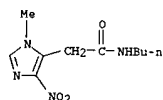


RN 252736-29-1 CAPLUS
 CN 1H-Imidazole-1-acetamide, N-[3-(fluoro-18F)propyl]-2-nitro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

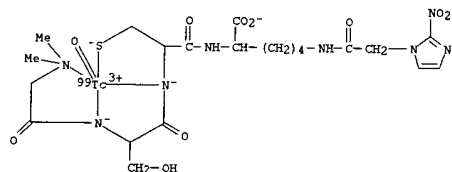
L11 ANSWER 20 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1999:612558 CAPLUS
 DOCUMENT NUMBER: 132:3337
 TITLE: Investigations on imidazoles. 99. Synthesis and some conversions of esters of 4-nitro-5-imidazolylmalonic, -acetoacetic, and -cyanoacetic acids
 AUTHOR(S): Kochergin, P. M.; Reznichenko, L. A.; Gireva, R. N.; Aleksandrova, E. V.
 CORPORATE SOURCE: Center for Drug Chemistry, All-Russian Research Institute for Pharmaceutical Chemistry, Moscow, 119815, Russia
 SOURCE: Chemistry of Heterocyclic Compounds (New York) (Translation of Khimiya Geterotsiklicheskih Soedinenii) (1999), 35(1), 51-57
 CODEN: CHCCAL; ISSN: 0009-3122
 PUBLISHER: Consultants Bureau
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 132:3337
 AB Title esters of 1-alkyl(1,2-dialkyl)-4-nitro-5-imidazolylmalonic, -acetoacetic, and -cyanoacetic acids were prepd. by treating 5-chloro(bromo)-1-alkyl(1,2-dialkyl)-4-nitroimidazoles with Et esters of carboxylic acids indicated. Some conversions of the compds. obtained have been studied, including ketone and acid decompn., synthesis of derivs. at the CO₂H and CO groups, and hydrogenation to 4-aminoimidazole derivs.
 IT 251297-89-9P
 RACT RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); (Reactant or reagent) (prepn. and reactions of esters of nitroimidazolylmalonic, -acetoacetic, and -cyanoacetic acids)
 RN 251297-89-9 CAPLUS
 CN 1H-Imidazole-5-acetamide, N-butyl-1-methyl-4-nitro- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

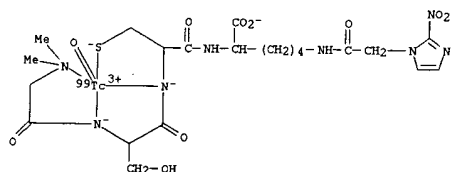
L11 ANSWER 21 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1999:539032 CAPLUS
 DOCUMENT NUMBER: 131:319697
 TITLE: Synthesis and Evaluation of Two Technetium-99m-Labeled Peptidic 2-Nitroimidazoles for Imaging Hypoxia
 AUTHOR(S): Su, Zi-Fen; Zhang, Xiguang; Ballinger, James R.; Rauth, A. M.; Pollak, Alfred; Thornback, John R.
 CORPORATE SOURCE: Departments of Medical Biophysics and Sciences, University of Toronto, Toronto, ON, M5G 2M9, Can.
 SOURCE: Bioconjugate Chemistry (1999), 10(5), 897-904
 CODEN: BOCHEB; ISSN: 1043-1802
 PUBLISHER: American Chemical Society
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The presence of hypoxic cells in solid tumors is a marker for therapy-resistant, aggressive disease. The noninvasive detection of hypoxic cells in tumors by radiolabeled 2-nitroimidazoles is a diagnostic technique under current evaluation. Two peptidic agents, dimethylglycyl-L-seryl-L-cysteinyll-lysyl(N.epsilon.-[1-(2-nitro-1H-imidazolyl)acetamido]glycine (RP435) and dimethylglycyl-tert-butylglycyl-L-cysteinyll-glycine-[2-(2-nitro-1H-imidazolyl)ethyl]amide (RP535) have been synthesized. Both agents contain an N3S class chelator for 99mTc and a 2-nitroimidazole group which can be enzymically reduced and selectively trapped in cells under hypoxic conditions. Two isomers of 99mTc-RP435, which are assumed to be syn and anti conformations, were obsd. on HPLC anal. The interconversion of the two isomers in aq. soln. was investigated. In contrast, RP535 chelated 99mTc to form a single isomer and no conversion to its counterpart has been obsd. on HPLC anal. The tert-Bu group on the chelator may inhibit the formation and interconversion of the syn and anti isomers of 99mTc-RP535. Both tracers showed a significant degree of hypoxia-specific accumulation in an in vitro assay, with 99mTc-RP535 showing higher selectivity for hypoxic cells than 99mTc-RP435. These results suggest that 99mTc-RP535 represents a lead compd. worthy of further investigation as an agent for imaging hypoxia in tumors.
 IT 247909-46-2P
 RACT RL: BPR (Biological process); BSU (Biological study, unclassified); (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses) (synthesis and evaluation of technetium-99m-labeled peptidic 2-nitroimidazoles for imaging hypoxia)
 RN 247909-46-2 CAPLUS
 CN Technetate(1-)-99Tc, [N,N-dimethylglycyl-.kappa.N-L-seryl-.kappa.N-L-cysteinyl-.kappa.N,.kappa.S-.kappa.N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-

L11 ANSWER 21 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 lysinato(4-)]oxo-, hydrogen, (SP-5-25)- (9CI) (CA INDEX NAME)



● H⁺

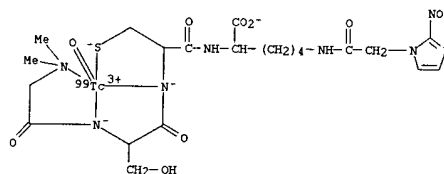
IT 247909-38-2P 247909-39-3P
 RL: PRP (Properties); PUR (Purification or recovery); SPN (Synthetic preparation); PREP (Preparation) (synthesis and evaluation of technetium-99m-labeled peptidic 2-nitroimidazoles for imaging hypoxia)
 RN 247909-38-2 CAPLUS
 CN Technetate(1-)-99Tc, [N,N-dimethylglycyl-.kappa.N-L-seryl-.kappa.N-L-cysteinyl-.kappa.N,.kappa.S-.kappa.N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-lysinato(4-)]oxo-, hydrogen, (SP-5-25-A)- (9CI) (CA INDEX NAME)



● H⁺

RN 247909-39-3 CAPLUS
 CN Technetate(1-)-99Tc, [N,N-dimethylglycyl-.kappa.N-L-seryl-.kappa.N-L-

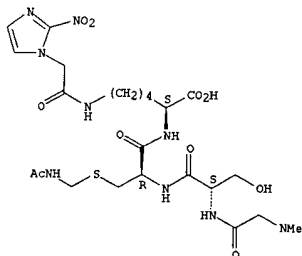
L11 ANSWER 21 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 cysteinyl-.kappa.N,.kappa.S-.kappa.N6-[(2-nitro-1H-imidazol-1-yl)acetyl]-L-lysinato(4-)]oxo-, hydrogen, (SP-5-25-C)- (9CI) (CA INDEX NAME)



● H⁺

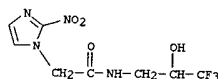
IT 248249-24-3P, RP 435
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (synthesis and evaluation of technetium-99m-labeled peptidic 2-nitroimidazoles for imaging hypoxia)
 RN 248249-24-3 CAPLUS
 CN L-Lysine, N,N-dimethylglycyl-L-seryl-S-[(acetylamino)methyl]-L-cysteinyl-N6-[(2-nitro-1H-imidazol-1-yl)acetyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



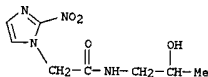
L11 ANSWER 21 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS
FORMAT RECORD. ALL CITATIONS AVAILABLE IN THE RE

L11 ANSWER 22 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:284037 CAPLUS
DOCUMENT NUMBER: 131:15726
TITLE: Preclinical development and current status of the fluorinated 2-nitroimidazole hypoxia probe N-(2-hydroxy-3,3,3-trifluoropropyl)-2-(2-nitro-1-imidazolyl)acetamide (SR 4554, CRC 94/17): a non-invasive diagnostic probe for the measurement of tumor hypoxia by magnetic resonance spectroscopy imaging, and by positron emission tomography. [Erratum to document cited in CA129:341244]
AUTHOR(S): Aboagye, Eric O.; Kelson, Andrew B.; Tracy, Michael; Workman, Paul
CORPORATE SOURCE: Dep. Radiol.-MR Res., The Johns Hopkins Univ. School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Anti-Cancer Drug Design (1998), 13(8), 1009-1010
PUBLISHER: CODEN: ACDDEA; ISSN: 0266-9536
DOCUMENT TYPE: Oxford University Press
LANGUAGE: Journal; General Review
AB The correct structure of the 2-nitroimidazole, EF5, is given.
IT 167648-73-9P, SR 4554
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses) (preclin. development and current status of the fluorinated 2-nitroimidazole hypoxia probe SR 4554, a non-invasive diagnostic probe for the measurement of tumor hypoxia (Erratum))
RN 167648-73-9 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)-(9CI) (CA INDEX NAME)



L11 ANSWER 23 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:5874 CAPLUS
DOCUMENT NUMBER: 130:206754
TITLE: TX-1877: design, synthesis, and biological activities
AUTHOR(S): as a BRM-functional hypoxic cell radiosensitizer
Yasuhiro: Kasai, Soko; Nagasawa, Hideko; Kuwasaka, Hideki; Oshodani, Tomoko; Nishioka, Akihito; Ogawa, Yoshida, Shoji; Inayama, Seiichi; Inomata, Taisuke; Hori, Hitoshi
CORPORATE SOURCE: Department of Biological Science and Technology, Faculty of Engineering, The University of Tokushima, Tokushima, 770-8506, Japan
SOURCE: International Journal of Radiation Oncology, Physics (1998), 42(4), 799-802
PUBLISHER: CODEN: IOBPDJ; ISSN: 0360-3016
DOCUMENT TYPE: Elsevier Science Inc.
LANGUAGE: Journal
AB 2-Nitroimidazole acetamide TX-1877 and its derivs. (TX-1877 analogs) were designed, synthesized, and evaluated by their in vitro and in vivo radiosensitization, tumor growth control, suppression of lung metastasis, and immunopotentialization, as biol. response modifier (BRM)-functional hypoxic cell radiosensitizers. TX-1877 analogs were designed and synthesized in our lab. In vitro radiosensitizing ability was estd. using EMT6/KU cells under hypoxic conditions. In vivo radiosensitization, antimetastasis, and immunopotentialization were evaluated using female C3H/He mice bearing the SCCVII tumor. Days (15 or 10) after the inoculation of 105 SCCVII tumor cells into the hinder thigh, a drug (0.4 mg/g) was administered i.p. and local irradiation of 30 Gy was given at 30 min after its administration. Tumor growth was obsd. for 20 days and mice were euthanized to count the no. of metastatic nodules on the surface of the lungs. Tumor tissues were extirpated and stained by the ABC method at 1, 2, and 3 wk after treatment for immunol. evaluation. Novel types of bifunctional radiosensitizers, TX-1877 and its analogs possessing BRM-functions (i.e., antimetastatic and immunopotentialization effects) were developed. In vitro radiosensitizing abilities of TX-1877 and its analogs, with their partition coeff. values of more than 0.050, were comparable to misonidazole (MISO) at their doses of 1 mM. Tumor regrowth was suppressed evidently 20 days after the treatment in the irradiated group with TX-1877 (TX-1877 plus R) and with KIN-806 (KIN-806 plus R).

L11 ANSWER 23 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
The former group reduced markedly the mean no. of metastatic lung nodules regardless of radiation therapy. TX-1877 and KIN-806 plus R induced helper T lymphocytes. The TX-1877, TX-1877 plus R, KIN-806, and KIN-806 plus R enhanced macrophage infiltration for 3 wk after treatment. TX-1877 is an excellent BRM-functional hypoxic cell radiosensitizer, expected to be useful for clin. use.
IT 220914-96-5P, TX 1909
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (design, synthesis, and biol. activities of TX-1877 analogs as BRM-functional hypoxic cell radiosensitizers)
RN 220914-96-5 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2-hydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)



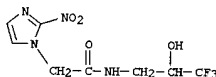
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS
FORMAT RECORD. ALL CITATIONS AVAILABLE IN THE RE

L11 ANSWER 24 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1998:622782 CAPLUS
 DOCUMENT NUMBER: 129:341244
 TITLE: Preclinical development and current status of the fluorinated 2-nitroimidazole hypoxia probe N-(2-hydroxy-3,3,3-trifluoropropyl)-2-(2-nitro-1-imidazolyl) acetamide (SR 4554, CRC 94/17): a non-invasive diagnostic probe for the measurement of tumor hypoxia by magnetic resonance spectroscopy and imaging, and by positron emission tomography

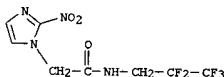
AUTHOR(S): Aboagye, Eric O.; Kelson, Andrew B.; Tracy, Michael;
 CORPORATE SOURCE: Workman, Paul
 University: Dep. Radiol.-MR Res., The Johns Hopkins School of Medicine, Baltimore, MD, 21205, USA
 SOURCE: Anti-Cancer Drug Design (1998), 13(6), 703-730
 CODEN: ACDDEA; ISSN: 0266-9536
 PUBLISHER: Oxford University Press
 DOCUMENT TYPE: Journal; General Review
 LANGUAGE: English
 AB A review with many refs. Hypoxia occurs to a variable extent in a vast majority of rodent and human solid tumors. It results from an inadequate and disorganized tumor vasculature, and hence an impaired oxygen delivery. A probe for the non-invasive detection of tumor hypoxia could find important utility in the selection of patients for therapy, with bioreductive agents, anti-angiogenic/anti-vascular therapies and hypoxia-targeted gene therapy. In addn., tumor hypoxia has been shown to predict for treatment outcome following radio- or chemotherapy in human cancers, the underlying mechanism for which may involve hypoxia driving genetic instability and resulting tumor progression. Beyond oncol., utility can also be envisaged in stroke, ischemic heart disease, peripheral vascular disease, arthritis and other disorders. Design, validation, preclin. development and current status of a fluorinated 2-nitroimidazole, N-(2-hydroxy-3,3,3-trifluoropropyl)-2-(2-nitro-1-imidazolyl) acetamide (SR 4554, CRC 94/17), which has been rationally designed for the measurement of tumor hypoxia by magnetic resonance spectroscopy (MRS) and imaging (MRI), are reviewed. Application in positron emission tomog. (PET) detection is also proposed. Design goals were: (i) a nitro group with appropriate redox potential for selective redn. and binding in hypoxic tumor cells; (ii) hydrophilic/hydrogen bonding character in the side chain to limit nervous tissue penetration and prevent neurotoxicity; and (iii) three equiv. fluorine atoms to enhance MRS/MRI detection, located in a metabolically stable position. Redn. of SR 4554 by mouse liver microsomes was dependent on oxygen

L11 ANSWER 24 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 REFERENCE COUNT: 99 THERE ARE 99 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
 FORMAT

L11 ANSWER 24 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 content, with a half-maximal inhibition at 0.49 +/- 0.06%. SR 4554 underwent nitroredn. by hypoxic but notoxic tumor cells in vitro and electron energy loss spectroscopic anal. showed selective retention in the hypoxic regions of multicellular tumor spheroids. Pharmacokinetic design goals were met. In particular, low brain tissue concns. were seen in contrast to excellent tumor levels, as measured by high performance liq. chromatog. The extent of this restricted entry to brain tumor was surprising given the overall octanol/water partition coeff. and was attributed to the hydrophilic/ hydrogen bonding character of the side chain. Quant. MRS was used to assess the retention of 19F signal in murine tumors and human tumor xenografts. The 19F retention index (FRI; ratio of 19F signal levels at 6 h relative to that at 45 min) ranged from 0.5 to 1.0 and 0.2 to 0.9 for murine tumors and human xenografts resp. The correlation between SR 4554 retention and pO2 was not a linear one, but when FRI was >0.5, the pO2 .ltoreq. 5 mmHg was always >60%, indicating that high FRI was assocd. with low levels of oxygenation. Finally, whole body 19F-MRI in mice demonstrated that SR 4554 and related metabolites localized mainly in tumor, liver and bladder regions. A selective MRS signal was readily detectable in tumors at doses at least 7-fold lower than those likely to cause toxicity in mice. We conclude that proof of principle is established for the use of SR 4554 as a non-invasive MRS/MRI probe for the detection of tumor hypoxia. Based on these promising studies, SR 4554 has been selected for clin. development.
 IT 167648-73-9P, SR 4554
 RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (preclin. development and current status of the fluorinated 2-nitroimidazole hypoxia probe SR 4554, a non-invasive diagnostic probe for the measurement of tumor hypoxia)
 RN 167648-73-9 CAPLUS
 CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)-(9CI) (CA INDEX NAME)



L11 ANSWER 25 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1998:589027 CAPLUS
 DOCUMENT NUMBER: 129:260386
 TITLE: An effective synthetic route to EF5
 AUTHOR(S): Baird, Ian R.; Skov, Kirsten A.; James, Brian R.; Rettig, Steven J.; Koch, Cameron J.
 CORPORATE SOURCE: Department of Chemistry, University of British Columbia, Vancouver, BC, V6T 1Z1, Can.
 SOURCE: Synthetic Communications (1998), 28(19), 3701-3709
 CODEN: SYNCAV; ISSN: 0039-7911
 PUBLISHER: Marcel Dekker, Inc.
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB EF5 (a 2-nitroimidazole contg. an N-(pentafluoropropyl)acetamide substituent) is a very sensitive probe for quantifying the amt. of hypoxia within cells: a much improved, short step, synthetic procedure is described for EF5, whose X-ray structure is also presented.
 IT 152721-37-4P, EF5
 RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation) (prepn. of (nitroimidazolyl)(pentafluoropropyl)acetamide)
 RN 152721-37-4 CAPLUS
 CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-(9CI) (CA INDEX NAME)

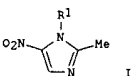


REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
 FORMAT

L11 ANSWER 26 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:184322 CAPLUS
DOCUMENT NUMBER: 128:286350
TITLE: 2-Methyl-5-nitroimidazoles and their use as inducers
INVENTOR(S): for endogenous antitumor activity
PATENT ASSIGNEE(S): Sugawara, Tsutomu; Kajitani, Tsutomu
SOURCE: Zaidanhojin Taishitsu Kenkyukai, Japan
Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JQXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 10077272	A2	19980324	JP 1996-234421	19960904
PRIORITY APPLN. INFO.:			JP 1996-234421	19960904
OTHER SOURCE(S):		MARPAT 128:286350		

GI

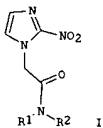


AB The title inducers contain 2-methyl-5-nitroimidazoles I [R1 = (CH2)a(CHOH)b(CH2)c[O(CH2)d]eH (a = 1-3; b, c = 0, 1; d = 0-3; e = 1-3; when d = 0, then e = 1), (CH2)fCO2(CH2)gH (f = 1-3; g = 0-3), (CH2)hCONH(CH2)i[O(CH2)j]kH (h = 1, 2; i = 0-6; j = 0-2; k = 0, 1)] as active ingredients and are administered at .ltoreq.1 mg/kg/time. Flagyl at 1 mg/kg/day for 20 days in total (10 days before and 10 days after inoculation of B16 melanoma cells) caused regression of the tumor cells in mice.
IT 205811-49-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (prepn. of 2-methyl-5-nitroimidazoles as inducers for endogenous antitumor activity)
RN 205811-49-0 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(3-hydroxypropyl)-2-methyl-5-nitro- (9CI) (CA INDEX NAME)

L11 ANSWER 27 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:165453 CAPLUS
DOCUMENT NUMBER: 128:192653
TITLE: Preparation of fluorinated 2-nitroimidazole analogs
INVENTOR(S): for detecting hypoxic tumor cells
Tracy, Michael; Kelson, Andrew B.; Workman, Paul; Lewis, Alexander D.; Aboagye, Eric O.
PATENT ASSIGNEE(S): SRI International, USA
SOURCE: U.S., 24 pp., Cont.-in-part of U.S. Ser. No. 286,477, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

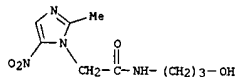
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5721265	A	19980224	US 1995-458178	19950602
CA 2196900	AA	19960215	CA 1995-2196900	19950731
WO 9604249	A1	19960215	WO 1995-US9611	19950731
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT,				
SE EP 775117	A1	19970528	EP 1995-927535	19950731
EP 775117	B1	20011121		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT,				
SE JP 10506104	T2	19980616	JP 1995-506660	19950731
AT 209187	E	20011215	AT 1995-927535	19950731
ES 2165430	T3	20020316	ES 1995-927535	19950731
PRIORITY APPLN. INFO.:			US 1994-286477	B2 19940805
			US 1995-458178	A 19950602
			WO 1995-US9611	W 19950731
OTHER SOURCE(S):		MARPAT 128:192653		

GI

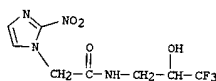


AB Title compds. I (R1, R2 = independently H, monosaccharide, alkyl, hydroxyalkyl, heterocycle) were prepd. to detect hypoxic tumor cells. Thus, I (R1 = H, R2 = CH2CH(OH)CF3) was prepd. and tested for detecting hypoxic tumor cells.

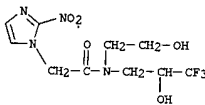
L11 ANSWER 26 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



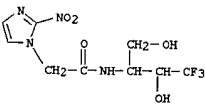
L11 ANSWER 27 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
IT 167648-73-9P 177595-17-4P 177595-20-9P
177595-21-0P 177595-22-1P 203452-63-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (prepn. of fluorinated nitroimidazole analogs for detecting hypoxic tumor cells)
RN 167648-73-9 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)- (9CI) (CA INDEX NAME)



RN 177595-17-4 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)- (9CI) (CA INDEX NAME)

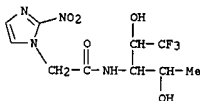


RN 177595-20-9 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxy-1-(hydroxymethyl)propyl)- (9CI) (CA INDEX NAME)

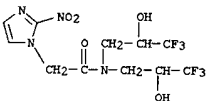


RN 177595-21-0 CAPLUS
CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxy-1-(1-hydroxyethyl)propyl)- (9CI) (CA INDEX NAME)

L11 ANSWER 27 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

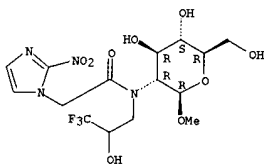


RN 177595-22-1 CAPLUS
CN 1H-imidazole-1-acetamide,
2-nitro-N-bis(3,3,3-trifluoro-2-hydroxypropyl)-
(9CI) (CA INDEX NAME)



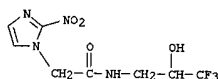
RN 203452-63-5 CAPLUS
CN .beta.-D-Glucopyranoside, methyl 2-deoxy-2-[(2-nitro-1H-imidazol-1-yl)acetyl] (3,3,3-trifluoro-2-hydroxypropyl)amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

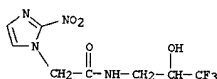


L11 ANSWER 29 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:752599 CAPLUS
DOCUMENT NUMBER: 128:70367
TITLE: Bioreductive metabolism of the novel fluorinated 2-nitroimidazole hypoxia probe
N-(2-hydroxy-3,3,3-trifluoropropyl)-2-(2-nitroimidazolyl) acetamide (SR-4554)
AUTHOR(S): Michael; Aboagye, Eric O.; Lewis, Alexander D.; Tracy, Workman, Paul
CORPORATE SOURCE: CRC DEPARTMENT OF MEDICAL ONCOLOGY, CLINICAL PHARMACOLOGY AND NEW DRUG DEVELOPMENT TEAM,
UNIVERSITY OF GLASGOW, GLASGOW, G61 1BD, UK
SOURCE: Biochemical Pharmacology (1997), 54(11),
1217-1224
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The aim of this work was to study the metabolic characteristics of the novel fluorinated 2-nitroimidazole hypoxia probe N-(2-hydroxy-3,3,3-trifluoropropyl)-2-(2-nitroimidazolyl) acetamide (SR-4554). HPLC and 19F NMR methods were employed to evaluate the rate of reductive metab. of SR-4554 and the nature of the resulting metabolites, resp. SR-4554 was enzymically reduced by mouse liver microsomes (1.1 +/- 0.1 nmol of SR-4554 reduced/min/mg protein), purified rat and human NADPH: cytochrome P 450 reductase (17.8 +/- 0.4 and 5.0 +/- 0.5 nmol of SR-4554 reduced/min/mg protein, resp.), and SCCVII tumor homogenates (2.3 +/- 0.3 nmol of SR-4554 reduced/min/g tumor) under nitrogen. NADPH:cytochrome P 450 reductase was a major microsomal enzyme involved in the bioredn. of SR-4554 by liver microsomes. In a panel of murine and human tumor xenografts, cytochrome P 450 reductase activities were found to be low and only varied by 3-fold between different tumor types, suggesting that enzyme activities within the tumors are unlikely to influence markedly in vivo reductive metab. Redn. of SR-4554 by mouse liver microsomes showed a characteristic oxygen dependence with a half-maximal inhibition of 0.48 +/- 0.06%. Thus, the reductive metab. of SR-4554 can be employed to detect the low oxygen tensions that occur within both murine and human tumors. Sol., low mol. wt. reductive metabolites of SR-4554 were identified by 19F NMR. These metabolite peaks appeared (up to 0.12 ppm) downfield of the parent drug peak. In conclusion, SR-4554 undergoes an

L11 ANSWER 28 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:87362 CAPLUS
DOCUMENT NUMBER: 128:202680
TITLE: The relationship between tumor oxygenation
determined by oxygen electrode measurements and magnetic resonance spectroscopy of the fluorinated 2-nitroimidazole SR-4554
Aboagye, E. O.; Maxwell, R. J.; Horsman, M. R.; Lewis, A. D.; Workman, P.; Tracy, M.; Griffiths, J. R.
CORPORATE SOURCE: Beatson Laboratories, CRC Department of Medical Oncology, Glasgow, G61 1BD, UK
SOURCE: British Journal of Cancer (1998), 77(1), 65-70
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The relationship between two methods of assessing tumor oxygenation in vivo, namely oxygen electrode measurement and magnetic resonance spectroscopy (MRS) of the fluorinated 2-nitroimidazole SR-4554, was investigated. Using three tumor models (two sites), no linear correlation was obsd. between 19F retention index and pO2 parameters (r .ltoreq. 0.3). Substantial retention of SR-4554 (19F retention index > 0.5) was, however, assocd. with low tumor pO2 (pO2 .ltoreq. 5 mmHg = 60%). Depending on the pO2 parameters used, SR-4554 administration was shown to produce either a significant or a non-significant increase in tumor oxygenation. The authors conclude that measurement of SR-4554-related compd. (s) by 19F-MRS has the potential to detect clin. relevant levels of tumor hypoxia.
IT 167648-73-9, SR-4554
RL: ARG (Analytical reagent use); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); USES (Uses) (relationship between tumor oxygenation detd. by oxygen electrode measurements and magnetic resonance spectroscopy of fluorinated 2-nitroimidazole SR-4554)
RN 167648-73-9 CAPLUS
CN 1H-imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)- (9CI) (CA INDEX NAME)



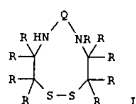
L11 ANSWER 29 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
oxygen-dependent metab. that involves NADPH:cytochrome P 450 reductase.
19F NMR is capable of identifying reduced metabolites that are undetectable by HPLC.
IT 167648-73-9, SR-4554
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process) (bioreductive metab. of hypoxia probe SR-4554)
RN 167648-73-9 CAPLUS
CN 1H-imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)- (9CI) (CA INDEX NAME)



L11 ANSWER 30 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1997:497147 CAPLUS
 DOCUMENT NUMBER: 127:202363
 TITLE: Preclinical evaluation of the fluorinated 2-nitroimidazole N-(2-hydroxy-3,3,3-trifluoropropyl)-2-(2-nitro-1-imidazolyl)acetamide (SR-4554) as a probe for the measurement of tumor hypoxia
 AUTHOR(S): Aboagye, Eric O.; Maxwell, Ross J.; Kelson, Tracy, Michael; Lewis, Alexander D.; Graham, Martin
 WORKMAN, A.; Horsman, Michael R.; Griffiths, John R.; Workman, Paul
 CORPORATE SOURCE: Cancer Res. Campaign, Dep. Medical Oncology, Beatson
 SOURCE: Labs., Glasgow, G61 1BD, UK
 PUBLISHER: Cancer Research (1997), 57(15), 3314-3318
 DOCUMENT TYPE: CODEN: CNREA8; ISSN: 0008-5472
 LANGUAGE: American Association for Cancer Research
 AB A novel probe, N-(2-hydroxy-3,3,3-trifluoropropyl)-2-(2-nitro-1-imidazolyl)acetamide (SR-4554), has been used to detect tumor hypoxia non-invasively by 19F magnetic resonance spectroscopy (19F MRS). The compd. was designed to undergo a hypoxia-dependent, one-electron redn. to metabolites that are selectively retained in tumors and has attractive pharmacokinetic, toxicol., and detection sensitivity properties. As a prelude to clin. studies, we report here for the first time on the ability to detect a MR signal following SR-4554 administration in various transplantable tumors and describe validation studies, consisting of a correlation between signal retention and radiobiol. hypoxic fraction, and the effects of modulating the degree of hypoxia by hydralazine and carbogen breathing. SR-4554 was absorbed and then eliminated from EMT6 tumors with a half-life of 51 min following an injection of 180 mg/kg i.p. of SR-4554. Using a quant. 19F MRS technique, the 19F retention index (19FRI; 19F signal level at 6 h/45 min) was detd. for four commonly used murine tumors (EMT6, SCCVII, KHT, and RIF-1). The retention of high concns. of fluorinated probe at 6 h, despite the much lower (20-fold) concn. of parent SR-4554 detected by high-performance liq. chromatog., was consistent with the involvement of one or more nitroreduced metabolites and suggested that 19F MRS might give a quant. measure of tumor hypoxia.

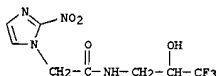
L11 ANSWER 31 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1997:204309 CAPLUS
 DOCUMENT NUMBER: 126:206814
 TITLE: Heteroatom-bearing bridged amine oxime ligands and analogs and their metal complexes for use in diagnostic and therapeutic methods
 INVENTOR(S): Ramalingam, Kondareddi; Raju, Natarajan
 PATENT ASSIGNEE(S): Bracco International B.V., Neth.
 SOURCE: U.S., 38 pp., Cont.-in-part of U.S.Ser.No. 77981, abandoned.
 DOCUMENT TYPE: USXXAM
 LANGUAGE: Patent
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION: English

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5608110	A	19970304	US 1994-242093	19940518
AT 165598	E	19980515	AT 1994-108968	19940610
ES 2115805	T3	19980701	ES 1994-108968	19940610
FI 9402795	A	19941216	FI 1994-2795	19940613
NO 9402231	A	19941216	NO 1994-2231	19940614
AU 9464672	A1	19941222	AU 1994-64672	19940614
AU 678001	B2	19970515		
ZA 9404201	A	19950208	ZA 1994-4201	19940614
CA 2125895	AA	19941216	CA 1994-2125895	19940615
CN 1099388	A	19950301	CN 1994-106661	19940615
CN 1055685	B	20000823		
JP 07089922	A2	19950404	JP 1994-133037	19940615
US 5627286	A	19970506	US 1995-472058	19950606
US 5656254	A	19970812	US 1995-471590	19950606
US 5665329	A	19970909	US 1995-480048	19950606
US 5741912	A	19980421	US 1995-479076	19950606
PRIORITY APPLN. INFO.:			US 1993-77981	B2 19930615
OTHER SOURCE(S):			US 1994-242093	A3 19940518
GI				

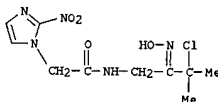


AB The invention provides for novel heteroatom-bearing bridged amine oxime ligands HON:CR¹CR²NR³-Q-NHCR⁴CR⁵:NOH, and the analogs disulfide-bridged cyclic compds. I and R1SCRR¹CR²NR³-Q-NHCR⁴CR⁵SR1 [Q = -(C(RR))m1-Y1-(C(RR))m2-(Y2-C(RR))m3]n-, where Y1 and Y2 = NR, O, S, SO, SO2, Se; n = 0,

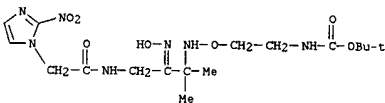
L11 ANSWER 30 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 In these murine tumors, 19FRI correlated with the reported radiobiol. hypoxic fraction of the tumors (r = 0.988). In addn., changes in tumor microenvironment were detected by 19F MRS. An increase in hypoxia induced by hydralazine treatment of RIF-1 tumor-bearing mice was assocd. with a 2.4-fold increase in 19FRI compared to untreated controls. In contrast, carbogen breathing by C3H mammary tumor-bearing mice produced a 6-fold decrease in the 19FRI compared to air-breathing mice. The data presented support the preclin. and clin. development of SR-4554 as a noninvasive probe for tumor hypoxia.
 IT 167648-73-9, SR-4554
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 as a (preclin. evaluation of the fluorinated 2-nitroimidazole SR-4554 probe for the measurement of tumor hypoxia)
 RN 167648-73-9 CAPLUS
 CN 1H-imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)-(9CI) (CA INDEX NAME)



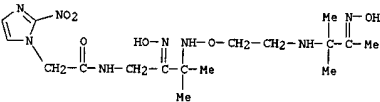
L11 ANSWER 31 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 1: m1, m2, m3 = 0-4 where m1 + m2 > 0; R and R' = R2, halo (esp. F), OR2, CO2R2, CON(R2)2, acyl, acyloxy, heterocyclo, hydroxyalkyl, etc., where a carbon atom bearing an R group is not directly bonded to more than one heteroatom; R1 = H, thiol protecting group, etc.; R2 = H, alkyl, alkenyl, alkynyl, aryl]. The invention provides for said amine oxime ligands above to contain a hypoxia-localizing moiety. The invention relates to complexes of these ligands, preferably with Re or Tc, which are useful in diagnostic and therapeutic methods. The invention relates further to kits for prep. the metal complexes. In preferred embodiments, the invention relates to complexes of these ligands which contain bioactive moieties, e.g., hypoxia-localizing moieties, which are capable of rapidly increasing ams. of a desired radionucleotide selectively to targeted areas. In an example, reaction of 1-(2-aminoethyl)-1-methylhydrazine (prepn. given) and 3-chloro-3-methyl-2-nitrosobutane in the presence of iPr2NET afforded HON:CHMeCH2NHC(CH3)2CH2NHC(CH3)2CH2NOH in 26% yield. Reaction of this ligand in saline with eluate from a 99Mo/Tc generator, followed by addn. of tin tartrate in saline afforded oxo[(3,3,5,9,9-pentamethyl-4,5,8-triazaundecanedioxiato)(3-)-N,N',N'',N''']technetium-99mTc(V) with >99% radiochem. purity (detd. after 5 min. at room temp.).
 IT 161490-39-7P 161490-40-0P 161490-41-1P
 167647-72-9P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (prepn. of heteroatom-bearing bridged amine oxime ligands, analogs, and their metal complexes for use in diagnostic or therapeutic methods)
 RN 161490-39-7 CAPLUS
 CN 1H-imidazole-1-acetamide, N-[3-chloro-2-(hydroxymino)-3-methylbutyl]-2-nitro- (9CI) (CA INDEX NAME)



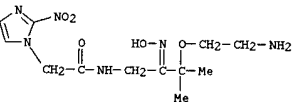
L11 ANSWER 31 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 RN 161490-40-0 CAPLUS
 CN 5-Oxa-2,6,10-triazadodecanoic acid,
 8-(hydroxyimino)-7,7-dimethyl-12-(2-
 nitro-1H-imidazol-1-yl)-11-oxo-, 1,1-dimethylethyl ester (9CI) (CA
 INDEX NAME)



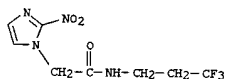
RN 161490-41-1 CAPLUS
 CN 1H-Imidazole-1-acetamide,
 N-[2-(hydroxyimino)-3-[[[2-(hydroxyimino)-1,1-
 dimethylpropyl]amino]ethoxy]amino]-3-methylbutyl]-2-nitro- (9CI) (CA
 INDEX NAME)



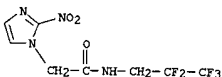
RN 187847-72-9 CAPLUS
 CN 1H-Imidazole-1-acetamide, N-[3-(2-aminoethoxy)-2-(hydroxyimino)-3-
 methylbutyl]-2-nitro- (9CI) (CA INDEX NAME)



L11 ANSWER 32 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



IT 152721-37-4P
 RL: ARG (Analytical reagent use); SPN (Synthetic preparation); THU
 (Therapeutic use); ANST (Analytical study); BIOL (Biological study);
 PREP (Preparation); USES (Uses)
 (hypoxia detection with 2-nitroimidazole compds. and immunogenic
 conjugates)
 RN 152721-37-4 CAPLUS
 CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-
 (9CI) (CA INDEX NAME)

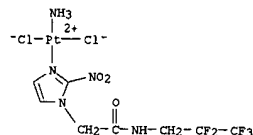


L11 ANSWER 32 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1996:494670 CAPLUS
 DOCUMENT NUMBER: 125:162343
 TITLE: Detection of hypoxia with reagents containing
 2-nitroimidazole compounds and methods of making
 such reagents
 INVENTOR(S): Koch, Cameron J.; Lord, Edith M.
 PATENT ASSIGNEE(S): The Trustees of the Univ. of Pennsylvania, USA;
 The University of Rochester
 SOURCE: U.S., 29 pp., Cont.-in-part of U.S. Ser. No.
 978,918, abandoned.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 3
 PATENT INFORMATION:

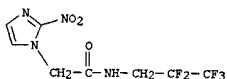
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5540908	A	19960730	US 1994-286065	19940804
CA 2149770	AA	19940526	CA 1993-2149770	19931118
US 5843404	A	19981201	US 1996-598752	19960208
US 6252087	B1	20010626	US 1998-123300	19980728
PRIORITY APPLN. INFO.:				
			US 1992-978918	B2 19921119
			US 1994-286065	A3 19940804
			US 1996-598752	A2 19960208

OTHER SOURCE(S): MARPAT 125:162343
 AB Novel nitroarom. compds. and immunogenic conjugates comprising a novel
 nitroarom. compd. and a carrier protein are disclosed. The invention
 further presents monoclonal antibodies highly specific for the claimed
 nitroarom. compds., protein conjugates of the compds., reductive
 byproducts of the compds., and adducts formed between the compds. and
 mammalian hypoxic cell tissue proteins. The invention is further
 directed to methods for detecting tissue hypoxia using immunohistol.
 techniques,
 noninvasive nuclear medicine methods (PET, SPECT), or NMR. Diagnostic
 kits useful in practicing the methods of claimed invention are also
 provided.
 IT 180208-73-5P
 RL: ARG (Analytical reagent use); SPN (Synthetic preparation); ANST
 (Analytical study); PREP (Preparation); USES (Uses)
 (hypoxia detection with 2-nitroimidazole compds. and immunogenic
 conjugates)
 RN 180208-73-5 CAPLUS
 CN 1H-Imidazole-1-acetamide, 2-nitro-N-(3,3,3-trifluoropropyl)- (9CI)
 (CA INDEX NAME)

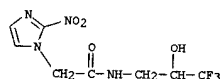
L11 ANSWER 33 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1996:492707 CAPLUS
 DOCUMENT NUMBER: 125:185094
 TITLE: Immunocytochemical labeling of aerobic and hypoxic
 mammalian cells using a platinated derivative of
 EFS
 AUTHOR(S): Matthews, J.; Adomat, H.; Farrell, N.; King, P.;
 Koch, C.; Lord, E.; Palcic, B.; Poulin, N.; Sangulin,
 J.; Skov, K.
 CORPORATE SOURCE: Department Medical Biophysics, BC Cancer Research
 Centre, Vancouver, BC, V5Z 1L3, Can.
 SOURCE: British Journal of Cancer, Supplement (1996),
 74(27),
 S200-S203
 CODEN: BJCSB5; ISSN: 0306-9443
 PUBLISHER: Stockton
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The monoclonal antibody ELK3-51 was previously developed to detect
 adducts
 of the 2-nitroimidazole EFS. Direct immunofluorescence was used to
 detect
 adducts of EFS or of a platinated deriv. cis-[PtCl2(NH3)EFS] in SCCVII
 cells treated under aerobic or hypoxic conditions. Fluorescence
 measurements of these cells using both image and flow cytometric
 methods
 were compared, giving similar profiles. Platination significantly
 decreased immunofluorescence levels (.apprx.4-fold less than EFS)
 after 3
 h in hypoxia, but also increased levels after exposure in air
 (.apprx.1.5
 times.) such that the hypoxic ratio decreased from .apprx.50 to
 .apprx.13. Platinated EFS also showed significantly greater
 cytotoxicity
 than its parent in both aerobic and hypoxic cells. These results are
 consistent with targeting of EFS to DNA, which was confirmed qual. by
 confocal microscopy.
 IT 180990-37-8
 RL: ANT (Analyte); BAC (Biological activity or effector, except
 adverse);
 BPR (Biological process); BSU (Biological study, unclassified); THU
 (Therapeutic use); ANST (Analytical study); BIOL (Biological study);
 PROC (Process); USES (Uses)
 (immunocytochem. labeling of aerobic and hypoxic mammalian cells
 using
 a platinated deriv. of EFS)
 RN 180990-37-8 CAPLUS
 CN Platinum, amminedichloro[2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-1H-
 imidazole-1-acetamide-N3]-, (SP-4-3)- (9CI) (CA INDEX NAME)



IT 152721-37-4
 RL: BFR (Biological process); BSU (Biological study, unclassified);
 BIOL (Biological study); PROC (Process)
 (immunocytochem. labeling of aerobic and hypoxic mammalian cells
 using a platinum deriv. of EF5)
 RN 152721-37-4 CAPLUS
 CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-
 (9CI) (CA INDEX NAME)



L11 ANSWER 34 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 (Process)
 (pharmacokinetics, bioavailability and biodistribution of tumor
 hypoxia probe SR-4554)
 RN 167648-73-9 CAPLUS
 CN 1H-Imidazole-1-acetamide,
 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)-
 (9CI) (CA INDEX NAME)

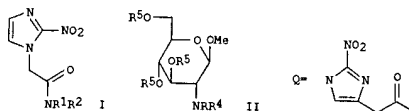


L11 ANSWER 34 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1996:427991 CAPLUS
 DOCUMENT NUMBER: 125:131550
 TITLE: The pharmacokinetics, bioavailability and biodistribution in mice of a rationally designed 2-nitroimidazole hypoxia probe SR-4554
 AUTHOR(S): Aboagye, Eric O.; Lewis, Alexander D.; Graham, A.; Tracy, Mike; Kelson, Andrew B.; Ryan, Kenneth J.;
 CORPORATE SOURCE: Workman, Paul
 CRC Department of Medical Oncology, University of Glasgow, Glasgow, G61 1 BD, UK
 SOURCE: Anti-Cancer Drug Design (1996), 11(3), 231-242
 CODEN: ACDDEA; ISSN: 0266-9536
 PUBLISHER: Oxford University Press
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB N-(2-Hydroxy-3,3,3-trifluoropropyl)-2-(2-nitro-1-imidazolyl) acetamide (SR-4554) is a fluorinated 2-nitroimidazole which has been rationally designed as non-invasive probe for tumor hypoxia. The key selection criteria for this mol. were low central nervous system penetration and toxicity, high metabolic stability other than nitroreduct., good tumor uptake and high sensitivity for detection by magnetic resonance spectroscopy. As part of the pre-clin. development strategy, pharmacokinetic, bioavailability and biodistribution studies were performed in mice. Pharmacokinetic studies in mice demonstrated that SR-4554 was rapidly absorbed into plasma following i.p. administration and eliminated with a half-life of 42 min, similar to other 2-nitroimidazoles. By comparing the areas under the concn.-time-curve (AUC), the tumor exposure towards SR-4554 was on av. 84% of the value obtained for the plasma exposure. SR-4554 penetrated tumor tissue extremely well but, in contrast to misonidazole and certain other fluorinated analogs, its distribution into brain tissue was poor (AUCbrain/AUCplasma = 0.07), suggesting potentially lower toxicity in spite of its higher lipophilicity (P = 0.43 vs. 0.63, resp.). The bioavailability of SR-4554 from i.p. and p.o. routes was 100 and 96% resp. In non-tumor-bearing mice, SR-4554 was excreted mainly as unchanged drug. The percentage of the injected p.p. dose of SR-4554 excreted unchanged in the urine over 24 h was 68.4%. Neither SR-4554 nor its metabolites were detected in mouse feces. We propose that these favorable pharmacokinetic properties of SR-4554 are due to the hydrophilic character and hydrogen-bonding capability of the amide and hydroxyl functions in the compd.
 IT 167648-73-9P, SR-4554
 RL: BFR (Biological process); BSU (Biological study, unclassified);
 SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation);
 PROC

L11 ANSWER 35 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1996:356969 CAPLUS
 DOCUMENT NUMBER: 125:34039
 TITLE: Preparation of fluorinated 2-nitroimidazole analogs
 INVENTOR(S): Tracy, Michael; Kelson, Andrew B.; Workman, Paul; Lewis, Alexander D.; Aboagye, Eric O.
 PATENT ASSIGNEE(S): Sri International, USA; University of Glasgow; Cancer
 SOURCE: Research Campaign Technology Limited
 PCT Int. Appl., 59 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

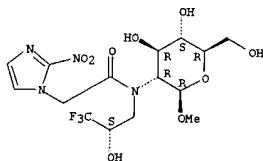
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9604249	A1	19960215	WO 1995-US9611	19950731
R: CA, JP				
US 5721265	A	19980224	US 1995-458178	19950602
EP 775117	A1	19970528	EP 1995-927535	19950731
EP 775117	B1	20011121		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 10506104	T2	19980616	JP 1995-506660	19950731
AT 209187	E	20011215	AT 1995-927535	19950731
PRIORITY APPLN. INFO.:				
			US 1994-286477	A 19940805
			US 1995-458178	A 19950602
			WO 1995-US9611	W 19950731

 OTHER SOURCE(S): MARPAT 125:34039
 GI

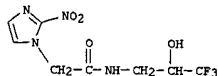


AB The title compds. [I; R1, R2 = H, monosaccharide (optionally functionalized to contain lower alkoxy, lower acyl, NH2, halo, or carboxylic acid moiety, wherein the linkage is to a carbon atom of the monosaccharide), lower alkyl substituted with CF3 and further substituted with at least one R3 (wherein R3 is selected from OH or optionally alkylated NH2), 5- or 6-membered heterocyclyl contg. one heteroatom selected from N, O, and S; or NRR1R2 = 5- or 6-membered heterocyclyl contg. one heteroatom selected from N, O, and S (wherein if the heteroatom is N,

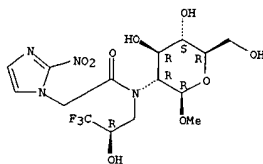
11 ANSWER 35 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

CC(F)(O)C(NC(=O)CN1C=CC(=N1)[N+](=O)[O-])COCN(C(C(=O)NCC1=CN=C(C=C1)[N+](=O)[O-])C(F)(F)F)C(O)C(F)(F)F

L11 ANSWER 35 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

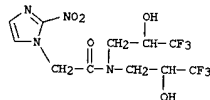
OCCN(Cc1cnc([N+](=O)[O-])n1)C(=O)NCC(C)C(F)(F)F

Absolute stereochemistry.

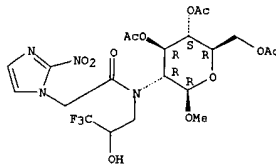


Absolute stereochemistry.

L11 ANSWER 35 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



Absolute stereochemistry.



L11 ANSWER 36 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1996:293265 CAPLUS
 DOCUMENT NUMBER: 125:4533
 TITLE: Biodistribution of the nitroimidazole EF5 (2-[2-nitro-1H-imidazol-1-yl]-N-(2,2,3,3,3-pentafluoropropyl)acetamide) in mice bearing subcutaneous EMT6 tumors

AUTHOR(S): Laughlin, K. M.; Evans, S. M.; Jenkins, W. T.; Tracy, M.; Chan, C. Y.; Lord, E. M.; Koch, C. J.
 CORPORATE SOURCE: Dep. Radn. Oncology, Univ. Pennsylvania, Philadelphia, PA, USA
 SOURCE: Journal of Pharmacology and Experimental Therapeutics
 (1996), 277(2), 1049-1057
 CODEN: JPETAB; ISSN: 0022-3565
 PUBLISHER: Williams & Wilkins
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The characteristic redn. and binding of nitroimidazoles to cellular macromols. in the absence of oxygen allows their use for detection and characterization of hypoxia. The biodistribution of a new nitroimidazole, EF5 (2-[2-nitro-1H-imidazol-1-yl]-N-(2,2,3,3,3-pentafluoropropyl)acetamide), in mice bearing EMT6 tumors is described. Detection methods based on radioactivity and monoclonal antibody techniques are compared for liver and tumor. All nonexcretory tissues demonstrated similar levels of radioactivity at 0.5 h postinjection of drug, demonstrating equiv. access of EF5 to all tissues. At 24 h, when unbound drug has been cleared, the tissues with the highest binding are the liver, esophagus, bladder and tumor. Typically, liver tissue contains the highest level of radio-activity at this time. Examn. of tumor and liver tissue by use of fluorescence microscopy and Cy3-bound monoclonal antibodies specific for EF5 adducts showed the patterns of binding in tumor are considerably more heterogeneous than those of liver. Histograms of fluorescence intensity, with use of these antibodies, demonstrate av. and maximal binding higher in tumors than in the liver. This divergence from the radioactivity data was detd. to be unrelated to sampling error, differential antibody access or staining efficiency of liver vs. tumor tissue. A possible cause is the scavenging of radioactive drug metabolites by liver. The data presented herein suggest that EF5 is useful as a hypoxia detector and that monoclonal antibody detection

L11 ANSWER 37 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1996:60562 CAPLUS
 DOCUMENT NUMBER: 124:139857
 TITLE: 2-Nitroimidazole (EF5) binding predicts radiation resistance in individual 9L s.c. tumors

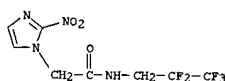
AUTHOR(S): Evans, Sydney M.; Jenkins, W. Timothy; Joiner, Barbara; Lord, Edith M.; Koch, Cameron J.
 CORPORATE SOURCE: Sch. of Veterinary Medicine, Univ. of Pennsylvania, Pennsylvania, PA, 19104, USA
 SOURCE: Cancer Research (1996), 56(2), 405-11
 CODEN: CNREAR; ISSN: 0008-5472
 PUBLISHER: American Association for Cancer Research
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The presence of hypoxic tumor cells cell is known to be an important cause of radiation treatment resistance in vivo. The ability to predict the presence and extent of hypoxic cells in individual tumors would allow the addn. of specific "antihypoxia"-based treatment regimes. Hypoxia can be monitored by measuring the binding of 2-nitroimidazoles. We have tested the hypothesis that binding of EF5, a fluorinated deriv. of the 2-nitroimidazole, Etanidazole, can predict radioreistance in individual tumors. Fischer rats bearing 9L s.c. tumors were given injections i.v. with EF5 3 h before irradiation and tumor harvest. Tumor cells were dissociated for flow cytometric anal. and plating efficiency studies. EF5 binding was detected via monoclonal antibodies conjugated to the orange emitting dye, Cy3. In air breathing rats, for a given radiation dose, a large amt. of variation in plating efficiency was seen. However, there was minimal variability of the plating efficiency for tumors irradiated in euthanized animals (hypoxic tumors; correlation coeff. for the fitted curve = 0.93) and in cells dissociated from tumors and irradiated in suspension (correlation coeff. for the fitted curve = 0.99), suggesting that varying sensitivity to the cell disaggregation technique was not responsible. In contrast, a good correlation between the relative radiation resistance or hypoxic survival and EF5 binding of "moderately" hypoxic cells in air breathing rats was identified using these techniques. In these 9L s.c. tumors, intertumor variation in oxygenation accounted for most of the range in individual tumor radiation response, and this was found to be independent of tumor size. This study provides evidence for the

L11 ANSWER 36 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 methods can give detailed information on the distribution of EF5 binding. This technol. may allow an accurate estn. of the oxygenation and/or nitroreductase levels in both tumor and normal tissues.

IT 152721-37-4
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (Biodistribution of nitroimidazole EF5 in tumor and liver and other tissues in relation to hypoxia detection)

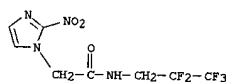
RN 152721-37-4 CAPLUS
 CN 1H-imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
 (CA INDEX NAME)



L11 ANSWER 37 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 application of EF5 binding with monoclonal antibody detection as an in vivo predictive assay of individual tumor hypoxia and resultant therapy resistance.

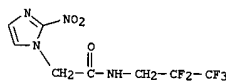
IT 152721-37-4
 RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
 (2-nitroimidazole (EF5) binding to tumor hypoxic fractions predicts x-ray resistance in individual 9L s.c. tumors)

RN 152721-37-4 CAPLUS
 CN 1H-imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)- (9CI)
 (CA INDEX NAME)



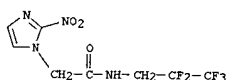
L11 ANSWER 38 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1995:1002637 CAPLUS
 DOCUMENT NUMBER: 124:52283
 TITLE: Mapping of the vascular endothelial growth factor-producing hypoxic cells in multicellular tumor spheroids using a hypoxia-specific marker
 AUTHOR(S): Waleh, Nahid S.; Brody, Michael D.; Knapp, Merrill A.; Mendonca, Holly L.; Lord, Edith M.; Koch, Cameron J.; Laderoute, Keith R.; Sutherland, Robert M.
 CORPORATE SOURCE: Cellular and Mol. Biol. Lab., Life Sci. Div., Menlo
 SOURCE: Park, CA, 94025, USA
 PUBLISHER: Cancer Research (1995), 55(24), 6222-6
 DOCUMENT TYPE: CODEN: CNREAS; ISSN: 0008-5472
 LANGUAGE: American Association for Cancer Research
 AB The authors have investigated the hypoxia inducibility of vascular endothelial growth factor (VEGF) in multicellular tumor spheroids of HT29 cells using a monoclonal antibody to a fluorinated bioreductive drug, EF5
 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide], a chem. probe for hypoxia. The authors have shown that VEGF expression is predominantly localized in interior spheroid cells that are sufficiently hypoxic to bioreductively activate the 2-nitroimidazole and produce immunol. detectable adducts of the EF5 compd. Northern blotting analyses demonstrated that VEGF165 is the predominant form of VEGF produced by HT29 cells and that the phorbol ester 12-O-tetradecanoylphorbol-13-acetate did not induce VEGF expression. This study demonstrates that VEGF expression is up-regulated in response to hypoxia and in the microenvironments found in human multicellular tumor spheroids. This investigation also illustrates the utility of the EF5 binding in multicellular tumor spheroids as a means of studying the expression and regulation of hypoxia-inducible genes.
 IT 152721-37-4
 RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
 (vascular endothelial growth factor expression colocalization with EF5 binding in hypoxic regions of multicellular tumor spheroids of human HT29 cells)
 RN 152721-37-4 CAPLUS
 CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-(9CI)

L11 ANSWER 38 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 (CA INDEX NAME)



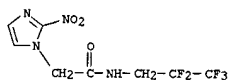
L11 ANSWER 39 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1995:936067 CAPLUS
 DOCUMENT NUMBER: 124:44585
 TITLE: Identification of hypoxia in cells and tissues of epigastric 9L rat glioma using EF5
 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl) acetamide]
 AUTHOR(S): Evans, S M.; Joiner, B.; Jenkins, W T.; Laughlin, K; M.; Lord, E M.; Koch, C J.
 CORPORATE SOURCE: Schools Veterinary Medicine (Clinical Studies), University Pennsylvania, Philadelphia, PA,
 19104, USA
 SOURCE: British Journal of Cancer (1995), 72(4), 875-82
 PUBLISHER: CODEN: BJCAAI; ISSN: 0007-0920
 DOCUMENT TYPE: Macmillan Scientific & Medical Division
 LANGUAGE: Journal
 AB One of the most sensitive hypoxia detection methods is based on the observation that binding of nitroimidazoles to cellular macromols. occurs as a result of hypoxia-dependent bioredn. by cellular nitroreductases. Nitroimidazole-binding techniques provide measurements of hypoxia to virtually and degree of spatial resoln. and with a multiplicity of techniques. This paper demonstrates hypoxia imaging using in vivo EF5 binding with detection by a fluorochrome-conjugated monoclonal antibody. The authors investigated these techniques in the 9L glioma tumor, in part because the exact nature of the hypoxia in this tumor system is controversial. The results demonstrate that following i.v. injection of EF5, binding and detection using a monoclonal antibody in 9L gliomas is specific and oxygen dependent. Detection of binding using fluorescence microscopy can be performed on frozen tissues; tissue sections can be counterstained with haematoxylin and eosin for light microscopic anal. Alternatively, the distribution of hypoxia in a tumor can be inferred by exang. individual tumor cells using flow cytometric techniques. Based upon the results presented herein, the radiation-resistant phenotype of 9L epigastric tumors grown in the labs. can be assocd. with the presence of hypoxic cells.
 IT 152721-37-4
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 (identification of hypoxia in cells and tissues of epigastric 9L rat glioma using EF5 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-

L11 ANSWER 39 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 pentafluoropropyl] acetamide])
 RN 152721-37-4 CAPLUS
 CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-(9CI)
 (CA INDEX NAME)



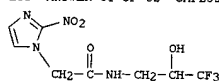
L11 ANSWER 40 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1995:936066 CAPLUS
 DOCUMENT NUMBER: 124:44665
 TITLE: Oxygen dependence of cellular uptake of EF5
 [2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide]: Analysis of drug
 adducts
 by fluorescent antibodies vs. bound radioactivity
 AUTHOR(S): Koch, C. J.; Evans, S. M.; Lord, E. M.
 CORPORATE SOURCE: Radiation Oncology, University Pennsylvania,
 Philadelphia, PA, 19104-6072, USA
 SOURCE: British Journal of Cancer (1995), 72(4), 869-74
 CODEN: BJCAAI; ISSN: 0007-0920
 PUBLISHER: Macmillan Scientific & Medical Division
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The present studies were initiated to quantitate the oxygen
 dependence of
 bioreductive metab.-induced binding of EF5, a pentafluorinated
 deriv. of
 the 2-nitroimidazole, etanidazole. Two different assays were
 compared:
 first, radioactive drug incorporation into cell lysates, which
 provides a
 direct measure of drug metab. or uptake; second, monoclonal antibody
 detection of cellular macromol. adducts of EF5 after whole cell
 permeabilization and fixing. The antibodies (a single clone
 designated
 ELK3-51) were conjugated with the fluorescent dye Cy3, with
 fluorescence
 detd. by fluorescence microscopy and flow cytometry. For the two
 cell
 lines tested (V79 Chinese hamster fibroblasts and 9L rat glioma), the
 oxygen dependence of binding was the same for the two techniques.
 Using
 the antibody binding technique, the fluorescence signal was highly
 reproducible between expts., resistant to light or chem. bleaching
 and
 stable over time following cell or tissue staining. Flow cytometric
 anal.
 of cells from rat 9L tumors treated with EF5 in vivo or in vitro
 showed a
 distribution of fluorescent signal which was very compatible, on
 both a
 relative and abs. basis, with the in vitro results. The results
 indicate
 that immunofluorescent techniques provide a quant. assay for
 bioreductive
 drug adducts, and therefore may be able to measure the abs. oxygen
 concn.
 distribution in cell populations and tissues of interest.
 IT 152721-37-4
 RL: BFK (Biological process); BSU (Biological study, unclassified);
 BIOL
 (Biological study); PROC (Process)
 (oxygen dependence of cellular uptake of EF5
 [2-(2-nitro-1H-imidazol-1-

L11 ANSWER 40 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 y1)-N-(2,2,3,3,3-pentafluoropropyl)acetamide): anal. of drug
 adducts by
 fluorescent antibodies vs. bound radioactivity)
 RN 152721-37-4 CAPLUS
 CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-
 (9CI)
 (CA INDEX NAME)



L11 ANSWER 41 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1995:865440 CAPLUS
 DOCUMENT NUMBER: 123:309596
 TITLE: Development and validation of a solid-phase
 extraction
 and high-performance liquid chromatographic
 assay for
 a novel fluorinated 2-nitroimidazole hypoxia
 probe
 (SR-4554) in Balb/c mouse plasma
 AUTHOR(S): Aboagye, E. O.; Graham, M. A.; Lewis, A. D.;
 Workman,
 P.; Kelson, A. B.; Tracy, M.
 CORPORATE SOURCE: Clinical Pharmacology and New Drug Development
 Team,
 CRC Department of Medical Oncology, University of
 Glasgow, CRC Beatson Laboratories, Alexander
 Stone
 Building, Gartcube Estate, Switchback Road,
 Glasgow,
 G61 1BD, UK
 SOURCE: Journal of Chromatography, B: Biomedical
 Applications
 (1995), 672(1), 125-32
 CODEN: JCEBEF; ISSN: 0378-4347
 PUBLISHER: Elsevier
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB
 N-(2-Hydroxy-3,3,3-trifluoropropyl)-2-(2-nitro-1-imidazolyl)acetamide, a
 novel 2-nitroimidazole, is currently being developed as a noninvasive
 probe for tumor hypoxia. A sensitive (min. quantifiable level = 25
 ng/mL;
 C.V. = 6.01%) and selective assay has, therefore, been developed for
 the
 anal. of this compd. in mouse plasma. The assay employed solid-phase
 extn. followed by a rapid (10 min) HPLC anal. with
 UV-photodiode-array
 detection. No drug-related metabolites were obsd. in plasma when
 mice
 were treated with 180 mg/kg of the drug. The assay was suitable for
 studying the plasma pharmacokinetics of this fluorinated
 2-nitroimidazole
 in mice.
 IT 167648-73-9, SR 4554
 RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study);
 BIOL
 (Biological study); USES (Uses)
 (extn. and HPLC assay of fluorinated 2-nitroimidazole hypoxia
 probe
 (SR-4554) in Balb/c mouse plasma)
 RN 167648-73-9 CAPLUS
 CN 1H-Imidazole-1-acetamide,
 2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)-
 (9CI) (CA INDEX NAME)

L11 ANSWER 41 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



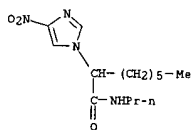
DOCUMENT TYPE: abandoned.
LANGUAGE: CODEN: USXXAM
FAMILY ACC. NUM. COUNT: Patent
PATENT INFORMATION: English
2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5401851	A	19950328	US 1993-49917	19930420
CA 2097462	AA	19930104	CA 1993-2097462	19930601
HU 64238	A2	19931228	HU 1993-1603	19930601
IL 105877	A1	19980715	IL 1993-105877	19930601
NO 5302005	A	19931206	NO 1993-2005	19930602
EP 173271	A1	19931208	EP 1993-304264	19930602
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT,				
SE AU 9339985	A1	19940120	AU 1993-39985	19930602
AU 667803	E2	19950119	RU 1993-46487	19930602
RU 2110515	C1	19980510	RU 1993-107578	19930603
CN 1085897	A	19940427		
CN 1045768	B	19991020		
JP 07304752	A2	19951121	JP 1993-133122	19930603
PL 173340	B1	19980227	PL 1993-299716	19930603
US 5484780	A	19960116	US 1994-355778	19941214
PRIORITY APPLN. INFO.:			US 1992-692867	R2 19920603
			US 1993-49917	A 19930420
OTHER SOURCE(S): MARPAT 123:257395				
GI				

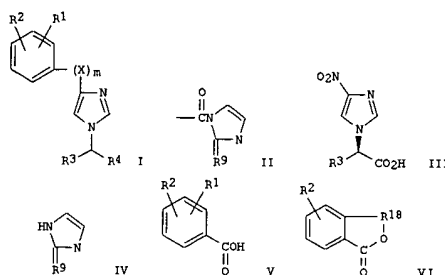
```

L11 ANSWER 42 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
    where XB = [molar concn. of antagonist]/([EC50 AIT with
antagonist]/EC50
    AIT without antagonist]-1)]) was evaluated in the rabbit aorta test
system: for VII, KI = 10.3 and pA2 = 5.7. Pharmaceutical
formulations
    were given.
IT 157187-22-9P
    RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
    (Reactant or reagent)
    (imidazolyl amino acid derivs. as angiotensin II antagonists)
RN 157187-22-9 CAPLUS
    CN 1H-Imidazole-1-acetamide, .alpha.-hexyl-4-nitro-N-propyl- (SCI)
INDEK (NAME)

```



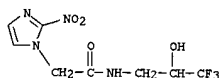
L11 ANSWER 42 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



AB A process of prepg. a substantially pure (R) enantiomer of the compd.
of the formula I wherein: R1 is CO₂H, SO₃H, PO₃H₂, CONHSO₂RS or
5-tetrazolyl;
R2 is H, OH, OCOCH₃, halo, C1-C4 alkyl, amino, acetamido, or C1-C4
alkenyl;
X is (CH₂)_mNHCO, (CH₂)_mCONH, O, NH, CH₂, (CH₂)_mCO, or CO(CH₂)_m; R3 is
C4-C9 straight chain alkyl, C4-C9 straight chain trifluoroalkyl, C4-C9
straight chain alkenyl, or C4-C9 straight chain trifluoroalkenyl; R4
is CONH(C1-C4 alkyl), CONH(C1-C4 trifluoroalkyl), CONH(hydroxy-C1-C4
alkyl),
or, e.g., I1; R5 is Ph, C1-C4 alkyl substituted Ph, C1-C5 alkyl, or
C1-C5 trifluoroalkyl; R9 is O or S; m is independently 0 or 1; p is
independently 0, 1, 2, 3 or 4; and q is 1, 2, 3, or 4 (with proviso);
comprising coupling a compd. of the formula III to, e.g., IV;
reducing the
nitro of the compd. of the formula III to produce an aminoimidazole;
coupling the aminoimidazole to V or VI (R18 = SO₂ or CO). Thus, e.g.,
reaction of 4-nitroimidazole with Et 2-bromooctanoate afforded Et
2-(4-nitro-1H-imidazol-1-yl)octanoate; reaction of the latter with
ethylamine afforded N-ethyl-2-(4-nitro-1H-imidazol-1-yl)octanamide;
N-ethyl-2-(4-nitro-1H-imidazol-1-yl)octanamide was reduced by
hydrogenation at 40 psi over Pd/C and the aminoimidazole was added to
a soln. of 2-sulfobenzoic acid cyclic anhydride to afford
N-ethyl-2-[4-(2-sulfenylamino)-1H-imidazol-1-yl]octanamide (VII).
The ability of I to block angiotensin II receptor binding (KI, .mu.M)
was detd. using the adrenal glomerulosa assay, and the ability to
antagonize
angiotensin-induced vasoconstriction [potency = pA₂ (defined as -log
KB.

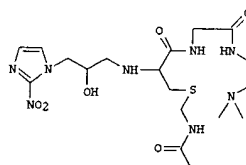
111 ANSWER 43 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:750169 CAPLUS
DOCUMENT NUMBER: 123:192723
TITLE: The novel fluorinated 2-nitroimidazole hypoxia
probe
SR-4554: reductive metabolism and semiquantitative
localization in human ovarian cancer multicellular
spheroids as measured by electron energy loss
spectroscopy analysis
AUTHOR(S): Aboagye, EO; Lewis, AD; Johnson, A.; Workman, P.
Tracy, M.; Huxham, I. M.
CORPORATE SOURCE: CRC Dep. of Medical Oncology, Univ. of Glasgow,
Glasgow, G61 1BD, UK
SOURCE: British Journal of Cancer (1995), 72(2), 312-18
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Macmillan Scientific & Medical Division
JOURNAL
LANGUAGE: English
AB The novel fluorinated 2-nitroimidazole SR-4554 is undergoing preclin.
development as a magnetic resonance spectroscopy and imaging probe for
hypoxic tumor cells. We have used electron energy loss spectroscopic
anal. (EELS) to show selective reductn. and differential subcellular
localization of SR-4554 in human ovarian multicellular spheroids.
SR-4554
was demonstrated to be metabolized by these A2780 cells under hypoxic
but not under normal aerobic cell culture conditions. The EELS technique
illustrated that the relative amt. of drug within the cytoplasm of
cells from both the inner region (150-160 .mu.m from edge) and outer edge
of the spheroid did not differ significantly after an initial 3 h incubation
with drug. In contrast, an 8-fold differential between the amt. of drug
retained in the cytoplasm (primarily ribosomes and endoplasmic
reticulum) of cells from the inner vs outer regions of the spheroids was obsd.
following a subsequent 2 h 'chase' culture in drug-free medium.
Within cells from the hypoxic region of the spheroid, SR-4554 was mainly
assocd. with the endoplasmic reticulum, nucleus and the cytoplasmic side of
intracellular vesicles and also to a lesser extent with the nuclear
periphery. Interestingly, the drug was only weakly assocd. with the
mitochondria and plasma membrane of the cells. The characteristics of
cellular and subcellular distribution of SR-4554 are consistent with
the hypothesis that 2-nitroimidazole compds. undergo hypoxia-mediated
enzymic reductn. to reactive species. These reactive species are selectively
retained in the cells in which they are metabolized through covalent
assocn. with subcellular components. These findings provide addn.
support for the clin. development of the drug as a non-invasive probe
for tumor hypoxia and at the same time illustrate the utility of the EELS
technique for examp. the heterogeneity of drug distribution both
between

L11 ANSWER 43 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
and within cells.
IT 167648-73-9, SR 4554
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES
(Uses)
(the fluorinated 2-nitroimidazole hypoxia probe SR-4554 and
reductive metab. and semiquant. localization in human ovarian cancer
multicellular spheroids as measured by electron energy loss
spectroscopy anal.)
RN 167648-73-9 CAPLUS
CN 1H-Imidazole-1-acetamide,
2-nitro-N-(3,3,3-trifluoro-2-hydroxypropyl)-
(9CI) (CA INDEX NAME)



L11 ANSWER 44 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:638235 CAPLUS
DOCUMENT NUMBER: 123:83362
TITLE: Preparation of metal chelating compounds.
INVENTOR(S): Archer, Colin Mill; Bower, Robert Gary; Gill,
Harjit
Kaur; Riley, Anthony Leonard Mark; Storey, Anthony
Eamon; Canning, Lewis Reuben; Griffiths, David
Vaughan
PATENT ASSIGNEE(S): Amersham International PLC, UK
SOURCE: Eur. Pat. Appl., 45 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

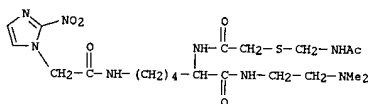
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 618191	A1	19941005	EP 1993-302634	19930402
R: BE, DE, ES, FR, GB, IT, NL, SE				
WO 9422816	A1	19941013	WO 1994-GB693	19940331
W: AU, CA, JP, US				
CA 2136970	AA	19941013	CA 1994-2136970	19940331
AU 9453822	A1	19941024	AU 1994-63822	19940331
AU 672894	B2	19961017		
JP 07507331	T2	19950810	JP 1994-521844	19940331
JP 2860166	B2	19990224		
US 5932707	A	19990803	US 1997-888398	19970707
US 6004531	A	19991221	US 1997-917476	19970826
PRIORITY APPLN. INFO.:			EP 1993-302634	19930402
			WO 1994-GB693	19940331
			US 1997-888398	19970707
OTHER SOURCE(S):		MARPAT 123:83362		
GI				



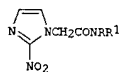
I

AB Ligands A(CR2)nB(CR2)mRN(CR2)nA', 2S(CR2)mXN(CR2)nXN(CR2)mY (A, A' =
ZS,
Y; B = O, S wherein Y = R(CR2)qNR, Z = H, thiol protectant; m, n =
2,3, q =
0,1; R = H, C1-20 alkyl, or alkenyl, or alkoxy, or alkoxyalkyl,
amide,

L11 ANSWER 44 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
amine, HO2C, HO-alkyl, aryl, or 2 R's of any R2C and/or 2 or more
adjacent
R2C may be combined to form C3-6 cycloalkyl, aryl, heteroaryl, etc.;
X =
R) and a salt thereof, are prep. The ligands and their resp.
radiometal
complexes can be bound to biol. targeting mols.
1-(2,3-Epoxypropyl)-2-
nitroimidazole in MeOH was to AcNHCH2SCH2CH(NH2)CONHCH2CONH(CH2)2NMe2
(prepn. given) in MeOH to give the title ligand (I). I was labeled
with
99mTc and the hypoxic and oxidic binding to cells in vitro shown.
IT 164213-58-5P
RL: BAC (Biological activity or effector, except adverse); BSU
(Biological
study, unclassified); SPN (Synthetic preparation); THU (Therapeutic
use);
BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of metal chelating compds.)
RN 164213-58-5 CAPLUS
CN 1H-Imidazole-1-acetamide,
N-[5-[[[[(acetylaminomethyl)thio]acetyl]amino]-
6-[[2-(dimethylamino)ethyl]amino]-6-oxohexyl]-2-nitro- (9CI) (CA
INDEX
NAME)

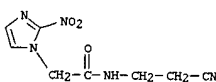


L11 ANSWER 45 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:525695 CAPLUS
DOCUMENT NUMBER: 123:313839
TITLE: Synthesis and polyamine derivatives of
2-nitroimidazole as DNA-directed radiosensitizers
Farrick, John; Forss, Manuchehr
Dep. Chem., Brunel Univ., Uxbridge, UB8 3PH, UK
Journal of Chemical Research, Synopses (1995),
(5),
186-7
CODEN: JRPSDC; ISSN: 0308-2342
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The synthesis of a series of 1-substituted amino deriva. of
2-nitroimidazole, via an improved route to
N-(aminoalkyl)-2-nitroimidazole-
1-ylacetamides I (R, R1 = H, aminoalkyl) was described. The
pharmacol.
activity of I was not reported here.
IT 165062-76-0P 165062-77-1P 165062-78-2P
165062-79-3P 165062-80-6P 165062-82-8P
165062-83-9P 165062-84-0P 165062-85-1P
165062-86-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
RACIT
(Reactant or reagent)
((aminoalkyl)nitro-1H-imidazoleacetamides DNA-directed
radiosensitizers)
RN 165062-76-0 CAPLUS
CN 1H-Imidazole-1-acetamide, N-(2-cyanoethyl)-2-nitro- (9CI) (CA INDEX
NAME)



RN 165062-77-1 CAPLUS
CN 1H-Imidazole-1-acetamide, N-[3-(dimethylamino)propyl]-2-nitro- (9CI)
(CA
INDEX NAME)

CN(C)CCCC(=O)CN1C=CC=C(C1)[N+](=O)[O-]CN(CCNCCc1cc([N+](=O)[O-])nn1)C(=O)NCCc2ccc([N+](=O)[O-])nn2O=[N+]([O-])c1ncnc1NCC(=O)NCCCCNCCCCNCCCC(=O)Nc1c[nH]c2ccccc12
$$\text{CH}_2\text{-C(=O)-NH-(CH}_2\text{)}_3\text{-NH-(CH}_2\text{)}_4\text{-NH-(CH}_2\text{)}_3\text{-NH-C(=O)-OEt}$$

CM 1

CRN 165062-81-7
CMF C15 H29 N7 O3

CCOC(=O)C(=O)N(CCC)N(CCC)C(=O)N(CCC)C(=O)Cc1c[nH]c2ccccc12CC(C)NCC(=O)CN1C=CC(=C1)[N+](=O)[O-]O=[N+]([O-])c1ccn(c1)CC(=O)NCCO=[N+]([O-])c1cc[nH]1CC(=O)NCCCCNCCCCNCCCCN

CH 2

CRN 76-05-1

CMF C2 H F3 02


$$\text{CH}_2\text{---C(=O)---N---(CH}_2\text{)}_4\text{---NH---(CH}_2\text{)}_3\text{---NH---C(=O)---O---tBu}$$

NO_2
 N
 CH_2
 C(=O)
 N
 $\text{(CH}_2\text{)}_4$
 NH
 $\text{(CH}_2\text{)}_3$
 NH
 C(=O)
 O
 tBu

O=[N+]([O-])c1cc[nH]1CC(=O)N(CCN)CCCN

RN 165062-85-1 CAPLUS
CN 12-Oxa-2,6,10-triazatetradecanoic acid, 13,13-dimethyl-6-[(2-nitro-1H-imidazol-1-yl)acetyl]-11-oxo-, 1,1-dimethylethyl ester (9CI) (CA
INDEX

CAPLUS COPYRIGHT 2003 ACS
 1995:410624 CAPLUS
 122:229306
 Heteroatom-bearing ligands and metal complexes thereof.

INVENTOR(S): Ramalingam, Kondareddiari; Raju, Natarajan
PATENT ASSIGNEE(S): Bristol-Myers Squibb So., USA
SOURCE: Eur. Pat. Appl., 76 pp.

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 629617	A1	19941221	EP 1994-108968	19940610
EP 629617	B1	19980429		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL,

PT,	SE	AT	ET	CT	DT	ES	FS	GS	GR	IE	IL	LL	LU	ME
AT	165598		E			19800515			1984-108968					19940610
ES	2115805		T3			19800701			1984-108968					19940610
FI	9402795		A			19941216			FI 1994-2795					19940610
IE	162231					19941216			NO 1994-2231					19940614
AU	9464762		A1			19941222			AU 1994-64762					19940614
AU	678001		B2			19970515								
ZA	9404201		A			19950208			ZA 1994-4201					19940614
ZA	2125895		AA			19941216			ZA 1994-2125895					19940615
CN	103308					19950301			CN 1994-106661					19940615
CN	1055685		B			20000823								
JP	07089922		A2			19950434			JP 1994-133037					19940615

PRIORITY APPLN. INFO.: US 1993-77981 A 19930615
OTHER SOURCE(S): MARPAT 122:229386
GI

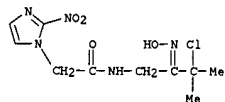
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Novel compds. contg. a heteroatom-bearing bridge (I, II, and III) and novel complexes of these compds. with metals are claimed. Details are given for the prepn. of dioxime ligands (I, Q = MeNCH₂CH₂, OCH₂CH₂, OCH₂CHCH₂) and their ^{99m}Tc complexes. The novel compds. and complexes

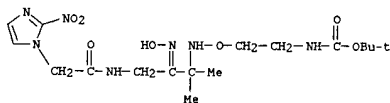
are useful as diagnostics and therapeutics.
IT 161490-39-7P 161490-40-0P 161490-41-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
RACT (Reactant or reagent)
(for prepn. of technetium triaza or oxadiazia dioxime complexes)

RN 161490-39-7 CAPLUS
CN 1H-Imidazole-1-acetamide,
N-[3-chloro-2-(hydroxyimino)-3-methylbutyl]-2-
nitro- (9CI) (CA INDEX NAME)

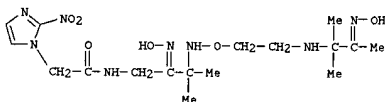
L11 ANSWER 46 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



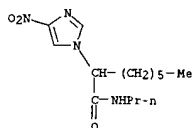
RN 161490-40-0 CAPLUS
CN 5-Oxa-2,6,10-triazadodecanoic acid,
8-(hydroxyimino)-7,7-dimethyl-12-(2-
nitro-1H-imidazol-1-yl)-11-oxo-, 1,1-dimethylethyl ester (9CI) (CA
INDEX NAME)



RN 161490-41-1 CAPLUS
CN 1H-imidazole-1-acetamide,
N-[2-(hydroxyimino)-3-[[2-[[2-(hydroxyimino)-1,1-
dimethylpropyl]amino]ethoxy]amino]-3-methylbutyl]-2-nitro- (9CI) (CA
INDEX NAME)

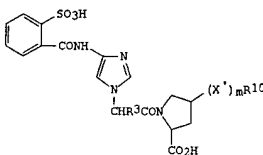


L11 ANSWER 47 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
pA2 vasoconstriction was evaluated in rabbit aorta test system where the
and of II was 6.6 and 6.7. A no. of imidazolyl derivs. were also prep.
evaluated. Pharmaceutical formulation of I are given.
IT 157187-22-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
RACT (Reactant or reagent)
RN (prepn. and reaction of, in prepn. of angiotensin II antagonists)
CN 157187-22-9 CAPLUS
CN 1H-imidazole-1-acetamide, .alpha.-hexyl-4-nitro-N-propyl- (9CI) (CA
INDEX NAME)



L11 ANSWER 47 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:558192 CAPLUS
DOCUMENT NUMBER: 121:158192
TITLE: Preparation of heterocycl-yl-substituted L-proline
as
INVENTOR(S): angiotensin II antagonists
Boyd, Donald Bradford; Hauser, Kenneth Lee; Lifer,
Sherryl Lynn; Marshall, Winston Stanley;
Palkowitz,
Alan David; Pfeiffer, William; Reel, Jon Kevin;
Simon,
Richard Lee; Steinberg, Mitchell Irvin; et al.
PATENT ASSIGNEE(S): Lilly, Eli, and Co., USA
SOURCE: Eur. Pat. Appl., 56 pp.
CODEN: EFXKDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 573271	A1	19931208	EP 1993-304264	19930602
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
US 5401851	A	19950328	US 1993-49917	19930420
PRIORITY APPLN. INFO.:			US 1992-892867	19920603
			US 1993-49917	A 19930420
OTHER SOURCE(S):			MARPAT 121:158192	
GI				

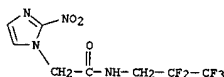


AB Title compds. I (R3 = C4-9 alkyl; R10 = p-(substituted) Ph, (substituted)
fused bicycyl or fused tricycyl; m = 0,1; X' = O, S (CH2)p wherein
p = 0-4) or a salt thereof, are prepd. (Me2CH)2NEt was added to D-proline
benzyl ester-HCl in DMF followed by
2-(4-nitro-1H-imidazol-1-yl)octanoic
acid to give a mixt of isomer esters which were reduced in EtOH with
Pd/C,
the catalyst filtered and to the product amine in THF was added
sulfobenzoic anhydride to give D-I (R3 = C6H13, (X')mR10 is nill) as 2
isomers (II). The ability to antagonize angiotensin-induced

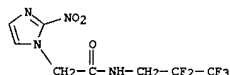
L11 ANSWER 48 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:506516 CAPLUS
DOCUMENT NUMBER: 121:106516
TITLE: Monoclonal antibody to nitroaromatic compound for
hypoxia detection
Koch, Cameron J.; Lord, Edith M.
PATENT ASSIGNEE(S): University of Pennsylvania, USA; University of
Rochester
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9411348	A1	19940526	WO 1993-US11190	19931118
W: CA, JP, LV, UZ				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2149770	AA	19940526	CA 1993-2149770	19931118
EP 669913	A1	19950906	EP 1994-902291	19931118
R: BE, CH, DE, DK, FR, GB, IT, LI				
JP 08503469	T2	19960416	JP 1993-512489	19931118
PRIORITY APPLN. INFO.:			US 1992-978918	A 19921119
			WO 1993-US11190	W 19931118
OTHER SOURCE(S):			MARPAT 121:106516	

AB Novel nitroarom. compds. and immunogenic conjugates comprising a novel
nitroarom. compd. and a carrier protein are disclosed. The invention
further presents monoclonal antibodies highly specific for the claimed
nitroarom. compds., the compds., protein conjugates, the compds.,
reductive byproducts, and adducts formed between the compds. and
mammalian
hypoxic cell tissue proteins. The invention is further directed to
methods for detecting tissue hypoxia using immunohistol. techniques,
non-invasive nuclear medicinal methods, or NMR. Diagnostic kits
useful in
practicing the methods of claimed invention are also provided.
IT 152721-37-4DP, conjugates with albumin or lysozyme or Bowman-Birk
inhibitor
RL: PREP (Preparation)
(prepn. of, as immunogen, for raising monoclonal antibody, for
hypoxia
detn.)
RN 152721-37-4 CAPLUS
CN 1H-imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-
(9CI)
(CA INDEX NAME)

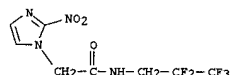


L11 ANSWER 48 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 IT 152721-37-4P
 RL: PREP (Preparation)
 (prepn. of, for prepn. immunogen for raising monoclonal antibody
 for hypoxia detn.)
 RN 152721-37-4 CAPLUS
 CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-
 (9CI)
 (CA INDEX NAME)

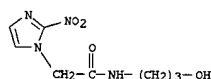


L11 ANSWER 49 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1994:101090 CAPLUS
 DOCUMENT NUMBER: 120:101090
 TITLE: Detection of hypoxic cells by monoclonal antibody recognizing 2-nitroimidazole adducts
 AUTHOR(S): Lord, Edith M.; Harwell, Lee; Koch, Cameron J.
 CORPORATE SOURCE: Cancer Cent., Univ. Rochester, Rochester, NY, 14642, USA
 SOURCE: Cancer Research (1993), 53(23), 5721-6
 CODEN: CNREA8; ISSN: 0008-5472
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB A pentafluorinated deriv. [EF5; 2-(2-nitro-1H-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)acetamide] of etanidazole was synthesized with the expectation of lessening some of the non-oxygen-dependent variability in adduct formation obsd. previously with other nitroarom. compds. EF5-protein conjugates, prepd. by radiochem. redn., were found to be immunogenic and allowed the development of monoclonal antibodies. One of these antibodies, ELK2-4, has been characterized and found to be highly specific for the EF5 adducts whether produced radiochem. or by cellular bioreductive metab. The 9L rat glioma cells pretreated with EF5 under hypoxic, compared with aerobic, conditions were readily discriminated immunochem. using fluorochrome-conjugated secondary antibodies which recognize the ELK2-4 antibody subtype (IgG1). Similarly, the central region of multicellular spheroids, composed of EMT6 mouse mammary sarcoma cells, was selectively visualized by immunohistochem. after the spheroids were incubated for 4 h in 0.5 mM EF5. Tumor biopsy, prepn., and immunohistochem. staining 24 h after treatment of tumor-bearing animals with drug also demonstrated high contrast regions within EMT6 mouse or Morris 7777 hepatoma rat tumors. The use of this new compd. and its highly specific monoclonal antibody may allow elucidation of bioreductive metab. of the nitroheterocyclics and significantly improve technologies for the quantitation of tissue pO2.
 IT 152721-37-4
 RL: ANST (Analytical study)
 (in hypoxic cell detection with monoclonal antibodies)
 RN 152721-37-4 CAPLUS
 CN 1H-Imidazole-1-acetamide, 2-nitro-N-(2,2,3,3,3-pentafluoropropyl)-
 (9CI)
 (CA INDEX NAME)

L11 ANSWER 49 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

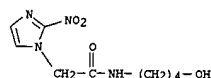


L11 ANSWER 50 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1992:608058 CAPLUS
 DOCUMENT NUMBER: 117:208058
 TITLE: Pharmacokinetics of fluorinated 2-nitroimidazole hypoxic cell radiosensitizers in murine peripheral nervous tissue
 AUTHOR(S): Sasai, K.; Iwai, H.; Yoshizawa, T.; Nishimoto, S.; Shibamoto, Y.; Kitakabu, Y.; Oya, N.; Takahashi, M.; Abe, M.
 CORPORATE SOURCE: Fac. Med., Kyoto Univ., Kyoto, 606, Japan
 SOURCE: International Journal of Radiation Biology (1992), 62(2), 221-7
 CODEN: IJURE7; ISSN: 0955-3002
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB KU-2285, a 2-nitroimidazole with a fluorinated N1-substituent (-CH2CF2CONH(CH2)nOH, n = 2), has been shown to be a promising hypoxic cell radiosensitizer. In this study, the pharmacokinetics of KU-2285 and its related compds. (n = 3 and n = 4) were compared with those of etanidazole [a 2-nitroimidazole with an N1-substituent of -CH2CONH(CH2)nOH, n = 2] and its related compds. (n = 3 and n = 4) to assess the effects of incorporation of a CF2 group. The lipophilicity of the fluorinated compds. was higher than that of etanidazole, as measured by the octanol/water partition coeff. As the no. of CH2 groups increased, the lipophilicity of the compds. in both the KU-2285 and etanidazole series increased. The brain tissue levels of the fluorinated compds. were as low as those of the etanidazole derivs., while the biol. half-lives of the fluorinated compds. in peripheral nervous tissues were shorter than those of related nonfluorinated compds.
 IT 144315-38-8, KU 3205 144315-39-9, KU 3206
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (pharmacokinetics of, as radiosensitizer, structure in relation to)
 RN 144315-38-8 CAPLUS
 CN 1H-Imidazole-1-acetamide, N-(3-hydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)



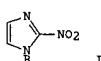
RN 144315-39-9 CAPLUS
 CN 1H-Imidazole-1-acetamide, N-(4-hydroxybutyl)-2-nitro- (9CI) (CA INDEX NAME)

L11 ANSWER 50 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
NAME)



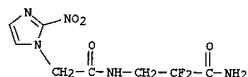
L11 ANSWER 51 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:6504 CAPLUS
DOCUMENT NUMBER: 114:6504
TITLE: Preparation of 3-(2-nitroimidazolo)-2,2-difluoropropionamides and analogs as
radiosensitizers
INVENTOR(S): Kagiya, Tautomu; Abe, Mitsuyuki; Nishimoto, Seichii;
Shibamoto, Yuta; Otomo, Susumu; Tanami, Tohru; Shimokawa, Kazuhiro; Yoshizawa, Toru; Hisanaga, Yorisato
PATENT ASSIGNEE(S): Nishijima, Yasunori, Japan; Taisho Pharmaceutical Co., Ltd.; Daikin Industries, Ltd.
SOURCE: Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 373630	A1	19900620	EP 1989-123062	19891213
CA 2005261	AA	19900614	CA 1989-2005261	19891212
US 4977273	A	19901211	US 1989-448909	19891212
AU 8946713	A1	19900621	AU 1989-46713	19891213
AU 625581	B2	19920716		
ZA 8909503	A	19900926	ZA 1989-9503	19891213
JP 02275863	A2	19901109	JP 1989-325437	19891214
PRIORITY APPLN. INFO.:			JP 1988-315974	19881214
OTHER SOURCE(S):			CASREACT 114:6504; MARPAT 114:6504	



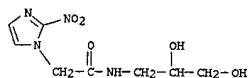
AB The title compds. [I; R = CH₂CFXCH₂OR₁; R₁ = CH₂CH(OR₂)CH₂OR₂, (CH₂)₁₀R₂, (CH₂)_m(CF₂)_n[CONH(CHR₃)r(CF₂)p]qZ, etc.; R₂ = H, OH (sic), alkyl, acyl; R₂₂ = PhCH, Me₂C; R₃ = H, alkyl; X = H, halo; Z = H, CO₂R₃, CO₂H, CONH₂, etc.; l = 1-3; m, n = 0-4; p = 0-2; q, r = 0-3] were prepd. as hypoxic cell sensitizers. Thus, I (R = CH₂CF₂CO₂Me) was stirred 1 h with H₂NCH₂CH₂CO₂Me.HCl in MeOH contg. KOH and the product stirred 2 days with aq. NH₃-MeOH contg. KOH to give I (R = CH₂CF₂CONHCH₂CH₂CONH₂) which gave cell-survival rate of EMT-6 tumor cells X-irradiated in mouse thigh

L11 ANSWER 51 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
664 that of unirradiated cells after administration of 100 mg/kg i.p.
IT 130777-35-49
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as radiosensitizer)
RN 130777-35-4 CAPLUS
CN 1H-Imidazole-1-acetamide,
N-(3-amino-2,2-difluoro-3-oxopropyl)-2-nitro-
(9CI) (CA INDEX NAME)



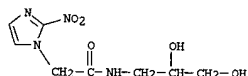
L11 ANSWER 52 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1983:449656 CAPLUS
DOCUMENT NUMBER: 99:49656
TITLE: Influence of heat on the intracellular uptake and radiosensitization of 2-nitroimidazole hypoxic cell
sensitizers in vitro
AUTHOR(S): Brown, Dennis M.; Cohen, Mark S.; Segerman, Robert H.; Gonzalez-Mendez, Ricardo; Hahn, George M.; Brown, J. Martin
CORPORATE SOURCE: USA
Sch. Med., Stanford Univ., Stanford, CA, 94305,
SOURCE: Cancer Research (1983), 43(7), 3138-42
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of elevated temp. (44.degree.) on the intracellular uptake of the 2-nitroimidazole hypoxic cell radiosensitizer, misonidazole (MIS), and analogs more hydrophilic than MIS was studied in Chinese hamster ovary cells. The intracellular uptake of these compds., which enter cells by restricted passive diffusion, can be enhanced .apprx.4-fold when incubated at 44.degree. compared to the uptake at 37.degree.. Peak intracellular uptake (expressed as the ratio of intracellular concn. to extracellular concn.) following incubation of cells in 2 mM MIS was 100% at 44.degree. but only 25% at 37.degree.. Furthermore, a short-term nonlethal heat pulse (44.degree. for 15 min) with MIS present caused a 2-fold enhancement in uptake which was sustained for an addnl. 45 min at 37.degree..
This same nonlethal heat pulse induced a similar enhancement in uptake even when MIS was added at subsequent time intervals at 37.degree.. The heat pulse induced a time-related enhancement of uptake at 37.degree. which increased for 1 h and persisted for at least 6 h. Finally, in vitro radiosensitization studies of hypoxic Chinese hamster ovary cells showed that the nonlethal heat pulse of 44.degree. for 15 min could greatly enhance the sensitization by low concns. (0.5 mM) of MIS added after heating due to increased intracellular concns. of the drug. MIS (0.5 mM) alone achieved a radiosensitization enhancement ratio of 1.29 (compared to irradiated hypoxic cells alone), whereas the addn. of the short-term heat pulse, which had only a minor effect itself, achieved an enhancement ratio of 1.78.
IT 74141-75-6

L11 ANSWER 52 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 RL: BIOL (Biological study)
 (metab. of and radiosensitization by, of CHO cells, heat effect
 on)
 RN 74141-75-6 CAPLUS
 CN 1H-imidazole-1-acetamide, N-(2,3-dihydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)



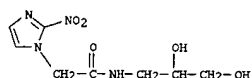
L11 ANSWER 53 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1983:122128 CAPLUS
 DOCUMENT NUMBER: 98:122128
 TITLE: Factors influencing intracellular uptake and radiosensitization by 2-nitroimidazoles in vitro
 AUTHOR(S): Brown, Dennis M.; Gonzalez-Mendez, Ricardo; Brown, J.
 CORPORATE SOURCE: Martin Sch. Med., Stanford Univ., Stanford, CA, 94305, USA
 SOURCE: Radiation Research (1983), 93(3), 492-505
 CODEN: RAREAE; ISSN: 0033-7587
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB The radiosensitization of hypoxic Chinese hamster ovary (HA-1) cells in vitro by misonidazole (MIS) and other 1-substituted 2-nitroimidazoles depends on the rate and extent of intracellular uptake of these radiosensitizers, which in turn is governed by their lipophilicity [expressed as the octanol:water partition coeff. (P)]. As the lipophilicity of the compds. decreased, the rate of drug entry into the cells was slower, and below P values of .apprx.0.05, peak intracellular drug concns. were lower than that of MIS (P = 0.43). In addn., the no. of hydroxyl groups on the side chain of the nitroimidazole mol. influenced the uptake of drug into the cells. For compds. of similar P, but differing in the no. of side-chain hydroxyl groups, the addn. of a single hydroxyl group to the mol. decreased the amt. of drug entering the cell by a factor of .apprx.2. These compds. enter the cell by nonmediated passive diffusion since altering the energy (ATP) capacity of the cell by 2-deoxyglucose did not affect uptake. Increases in temp. or decreases in pH can increase the intracellular uptake of MIS. For example, equal intracellular and extracellular concns. (100% uptake) of MIS were obtained if cells were heated to 44-45.degree. for 15 min compared to 20-40% uptake at 37.degree.. Increases in MIS uptake by factors of 2-3 could be demonstrated within 30 min when cells were incubated in Hanks' balanced salt soln. at pH 6.0-6.3 without loss of cell viability. In addn., MIS uptake in aerobic cultured cells varied 15-60%, depending on the cell line and culture conditions used.
 IT 74141-75-6
 RL: BIOL (Biological study)
 (metab. of and radiosensitization by, of CHO cells in vitro)
 RN 74141-75-6 CAPLUS
 CN 1H-imidazole-1-acetamide, N-(2,3-dihydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)

L11 ANSWER 53 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



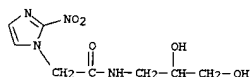
L11 ANSWER 54 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1983:83220 CAPLUS
 DOCUMENT NUMBER: 98:83220
 TITLE: Structure/activity relationships for the enhancement of electron-affinic drugs of the anti-tumor effect of CCNU
 AUTHOR(S): Workman, P.; Twentymann, P. R.
 CORPORATE SOURCE: MRC Clin. Oncol. Radiother. Unit, MRC Cent., Cambridge, CB2 2H, UK
 SOURCE: British Journal of Cancer (1982), 46(2), 249-59
 CODEN: BJCAAI; ISSN: 0007-0920
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB By means of a regrowth-delay assay, structure/activity relations for the enhancement by electron-affinic agents of the antitumor effect of the nitrosourea CCNU [13010-47-4] against the KHT sarcoma in C3H mice were investigated. A series of neutral 2-nitroimidazoles similar in electron affinity but varying in octanol:water partition coeff. (PC) over 4 orders of magnitude were examd. at a fixed dose of 2.5 mmol/kg. A parabolic (quadratic) dependence of activity on log PC was obsd. Analogs more hydrophilic than misonidazole (MISO) [13551-87-6] were inactive, as were those with very high PCs (>20). Those with PC 0.43-20 were usually more active than MISO. The fairly lipophilic 5-nitroimidazoles nimorazole [6506-37-2] and metronidazole (METRO) [443-48-1] had activity similar to that of MISO, despite their reduced electron affinity. Two basic 2-nitroimidazoles more efficient as radiosensitizers in vitro likewise showed activity comparable to MISO. Several agents more electron-affinic than MISO, including some nonnitro compds., were also investigated. Most of these agents were inactive at max. tolerated doses, but nitrofurazone [59-87-0] showed reasonable activity. Sensitizer dose-response curves were obtained for MISO, METRO, and two of the most effective agents, benznidazole [22994-85-0] and Ro 07-1902 [68160-71-4]. The latter 2 agents were both considerably more active than MISO at low doses (0.1-0.9 mmol/kg). Apparently, the structural features of electron-affinic agents responsible for the enhancement of KHT tumor response to CCNU are quite different from those affecting radiosensitization, lipophilicity being particularly important. The microsomal enzyme inhibitor SKF 525A [62-68-0] increased the antitumor effect of CCNU, suggesting inhibition of CCNU metab. as 1 possible mechanism contributing to chemosensitization by lipophilic electron-affinic agents in mice.

L11 ANSWER 54 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 IT 74141-75-6
 RL: BAC (Biological activity or effector, except adverse); BSU
 (Biological study, unclassified); BIOL (Biological study)
 (antitumor activity of CCNU response to, structure in relation to)
 RN 74141-75-6 CAPLUS
 CN 1H-Imidazole-1-acetamide, N-(2,3-dihydroxypropyl)-2-nitro- (9CI) (CA
 INDEX NAME)

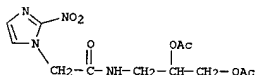


L11 ANSWER 55 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1982:213378 CAPLUS
 DOCUMENT NUMBER: 96:213378
 TITLE: Structure-activity relationships of 1-substituted
 2-nitroimidazoles: effect of partition
 coefficient and side-chain hydroxyl groups on
 radiosensitization in vitro
 AUTHOR(S): Brown, D. M.; Parker, E.; Brown, J. M.
 CORPORATE SOURCE: Sch. Med., Stanford Univ., Stanford, CA, 94305,
 USA
 SOURCE: Radiation Research (1982), 90(1), 98-108
 CODEN: RAREAE; ISSN: 0033-7587
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Fourteen 1-substituted 2-nitroimidazoles that ranged in lipophilicity
 with partition coeffs. (P) of 0.014-2.75 and that varied in the no. of OH
 groups (0-3) on the side chain at the 1-position of the nitroimidazole
 ring were studied for their ability to radiosensitize hypoxic Chinese
 hamster ovary cells (HA-1) in vitro. The concn. (Cl.6) of each compd.
 required for achieving an enhancement ratio (ER) of 1.6 was plotted
 as a function of P. Multiple linear regression analyses were performed to
 det. the influence of P and the no. of OH groups according to the equation
 $\log Cl.6 = b_0 + b_1 \log P + b_2 (\log P)^2 + b_3 (OH)$. Either independent
 variable log P or $(\log P)^2$ was significantly nonzero, and, if used sep. in the
 equation without the OH group term, could account for 51% of the
 explained variance (r^2) in the fit of the data. The no. of OH groups on the
 side chain affected radiosensitization or to a greater extent than P in the
 range presently studied (r^2 for the OH term alone was 0.58). An
 increase in OH group no. by 1 with no change in lipophilicity resulted in an
 increase in drug concn. needed for the equiv. radiosensitization by a
 factor of 2. The use of either the log P or $(\log P)^2$ terms together
 with the OH group term increased the r^2 value to 0.70. These data are
 relevant to the development of radiosensitizers potentially superior to
 misonidazole for clin. use, since they show that lipophilicity can
 only be decreased to .apprx.10% of that of misonidazole without producing a
 loss of radiosensitizing effectiveness, and that independent of
 lipophilicity, the addn. of OH groups to the mol. also reduces the radiosensitizing
 effectiveness.
 IT 74141-75-6 81892-65-1 81892-66-2
 81892-68-4
 RL: BIOL (Biological study)
 (radiosensitization by, structure in relation to)

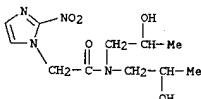
L11 ANSWER 55 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 RN 74141-75-6 CAPLUS
 CN 1H-Imidazole-1-acetamide, N-(2,3-dihydroxypropyl)-2-nitro- (9CI) (CA
 INDEX NAME)



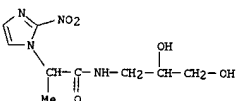
RN 81892-65-1 CAPLUS
 CN 1H-Imidazole-1-acetamide, N-[2,3-bis(acetyloxy)propyl]-2-nitro-
 (9CI) (CA
 INDEX NAME)



RN 81892-66-2 CAPLUS
 CN 1H-Imidazole-1-acetamide, N,N-bis(2-hydroxypropyl)-2-nitro- (9CI)
 (CA
 INDEX NAME)



RN 81892-68-4 CAPLUS
 CN 1H-Imidazole-1-acetamide,
 N-(2,3-dihydroxypropyl)-.alpha.-methyl-2-nitro-
 (9CI) (CA INDEX NAME)



L11 ANSWER 55 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

L11 ANSWER 56 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1982:42966 CAPLUS
DOCUMENT NUMBER: 96:42966
TITLE: Polarographic analysis of heterocyclic nitrogen compounds
AUTHOR(S): Leach, Steven C.; Weaver, Robert D.; Kinoshita, Kinio
CORPORATE SOURCE: Lee, William W.
SRI Int., Menlo Park, CA, 94025, USA
SOURCE: Journal of Electroanalytical Chemistry and Interfacial Electrochemistry (1981), 129(1-2), 213-27
CODEN: JEIEBC; ISSN: 0022-0728

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A correlation between the redn. potential of heterocyclic compds. and their effectiveness as radiosensitizing agents in cancer therapy has been

reported. This correlation provides a guide for evaluating the effectiveness of newly synthesized compds. as radiosensitizers. The half-wave redn. potential (E1/2) of selected nitroimidazoles, nitrotriazoles and heterocyclic amine N-oxides was measured at a dropping

Hg electrode in a Britton-Robinson buffer, pH 7.4. The effect of various substituent groups on the half-wave redn. potential of the heterocyclic compds. was investigated and the results are compared with published data.

A single redn. wave was obsd. with the nitroimidazoles and nitrotriazoles, whereas multiple redn. waves were obsd. with several of

the N-oxides of pyridine, quinoxaline and phenazine. When electron-attracting substituents were attached to the heterocyclic ring on

nitroimidazole and nitrotriazole, the redn. of the nitro group was easier

and E1/2 shifted in the pos. direction relative to that of the parent compd.

IT 74141-75-6

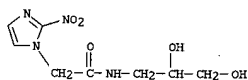
RL: PRP (Properties)

(neoplasm inhibitor, for carcinoma, elec. redn. potential in relation

to)

RN 74141-75-6 CAPLUS

CN 1H-Imidazole-1-acetamide, N-(2,3-dihydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)



L11 ANSWER 56 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

L11 ANSWER 57 OF 62 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1981:473052 CAPLUS
DOCUMENT NUMBER: 95:73052
TITLE: Pharmacokinetic considerations in radiosensitizer development
AUTHOR(S): Brown, J. Martin; Lee, William W.
CORPORATE SOURCE: Sch. Med., Stanford Univ., Stanford, CA, USA
SOURCE: Radiat. Sensitizers: Their Use Clin. Manage.
Cancer,

[Proc. Conf.] (1980), Meeting Date 1979, 2-13.

Editor(s): Brady, Luther W. Masson USA: New

York, N.

Y.

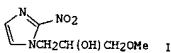
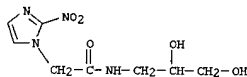
CODEN: 450JAG

DOCUMENT TYPE: Conference

LANGUAGE: English

GI

L11 ANSWER 57 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)



AB Tissue distribution and pharmacokinetic studies on 10 nitroimidazole radiosensitizers showed that there are compds. which have the same electron affinity and the same ability to radiosensitize hypoxic tumor

cells in vivo as misonidazole (I) [13551-87-6], but are less toxic

to mice. This reduced toxicity was correlated with a decreased ability

of the compds. with a decreased ability of the compds. to cross the

blood-brain barrier indicating these drugs to be less neurotoxic

than I. While the lipophilicity and partition coeff. of these drugs reflected

their ability to permeate the blood-brain barrier, the tumor-plasma

ratio was largely independent of the lipid soly.-or the partition coeff.

The concn. of SR-2555 [74141-74-5], a hydrophilic drug, in the hypoxic

cells was as good as that of I. Thus, the main disadvantage of these

agents compared to I was poor absorption after i.p. and oral administration.

IT 74141-75-6

RL: BAC (Biological activity or effector, except adverse); BSU

(Biological study, unclassified); BIOL (Biological study)

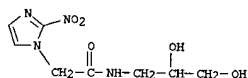
(radiosensitizing activity of, pharmacokinetics in relation to)

RN 74141-75-6 CAPLUS

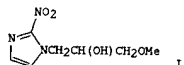
CN 1H-Imidazole-1-acetamide, N-(2,3-dihydroxypropyl)-2-nitro- (9CI) (CA

INDEX NAME)

L11 ANSWER 58 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1981:150996 CAPLUS
 DOCUMENT NUMBER: 94:150996
 TITLE: Radiosensitization of hypoxic bacterial cells by nitroimidazoles of low lipophilicity:
 steady-state
 AUTHOR(S): and rapid-mix studies
 Anderson, Robert F.; Patel, Kantilal B.; Sehmi, Darshan S.
 CORPORATE SOURCE: Cancer Res. Campaign Gray Lab., Mount Vernon Hosp.,
 Middlesex, HA6 2RN, UK
 SOURCE: Radiation Research (1981), 85(3), 496-504
 CODEN: RAREAE; ISSN: 0033-7587
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Radiosensitization of hypoxic bacterial cells by five 2-nitroimidazoles, with similar redn. potentials to misonidazole [13551-87-6] but having lower lipophilicities, has been measured in Escherichia coli AB 1157 and Streptococcus lactis 712. Sensitization efficiency progressively decreased with decreasing lipophilicity in E. coli but no in S. lactis. This difference is discussed in terms of the differing membrane properties of the 2 bacteria; E. coli resembled a multicompartiment model, as would also be expected with mammalian cells. Rapid-mix expts. are described which show that the radiosensitization obsd. after preirradn. contact times during .apprx.3-30 ms is dependent on the lipophilicity of the sensitizer, higher lipophilicity resulting in a lower contact time being required for radiosensitization. This result and the observation that a highly lipophilic compd. affects only half the full O enhancement level after short contact times suggest that part of the sensitization process occurs in a lipophilic (membrane) compartment of the cell.
 IT 74141-75-6
 RL: PRP (Properties) (radiosensitization by, of bacteria, lipophilicity in relation to)
 RN 74141-75-6 CAPLUS
 CN 1H-Imidazole-1-acetamide, N-(2,3-dihydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)



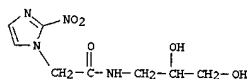
L11 ANSWER 59 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1980:461024 CAPLUS
 DOCUMENT NUMBER: 93:61024
 TITLE: Partition coefficient as a guide to the development of
 radiosensitizers which are less toxic than misonidazole
 AUTHOR(S): Brown, J. Martin; Workman, Paul
 CORPORATE SOURCE: Clin. Oncol. Radiotherapeut. Unit, MRC, Cambridge, UK
 SOURCE: Radiation Research (1980), 82(1), 171-90
 CODEN: RAREAE; ISSN: 0033-7587
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB Ten 2-nitroimidazole radiosensitizers of electron affinity equal to that of misonidazole (I), but differing in their octanol:water partition coeff. (P) over a 100-fold range, were chosen to examine the effect of lipophilicity on the pharmacokinetics of these drugs in BALB/c mice bearing EMT6 tumors. Plasma, tumor, and brain concns. were assayed as a function of time after a single i.p. injection of each drug. Peak concns. in the tumor declined with decreasing lipophilicity (decreasing P), but this was due to declining peak plasma concns. resulting from slower drug absorption and could be overcome by i.v. injection. The tumor/plasma ratio, once sufficient time had elapsed for it to reach its equil. value, was independent of P over the range 0.026-1.5 but showed a 50% redn. in this ratio for the most hydrophilic compd. studied (P = 0.014). This compd. was also the one drug in the series which was significantly poorer than I in its radiosensitization as a function of drug concn. The brain/plasma ratio, on the other hand, showed a marked dependence on lipophilicity. For I and more lipophilic compds., the brain/plasma ratio was 1.0, but as the lipophilicity decreased below that of I, the compds. showed an increasing difficulty in penetration into the brain, and brain/plasma ratios correlated with an increased acute LD50 of the drugs.

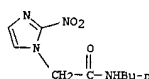
L11 ANSWER 58 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

L11 ANSWER 59 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 Bilateral nephrectomy was used to increase the apparent plasma half-life of SR-2508 [22668-01-5] from 0.8 to 15 h. This change, however, did not affect the tumor-brain ratio of .apprx.10 for this drug. These pharmacokinetic data are discussed in terms of the development of a radiosensitizer superior to I for clin. use.
 IT 74141-75-6
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (pharmacokinetics and toxicity of, partition coeffs. in relation to)
 RN 74141-75-6 CAPLUS
 CN 1H-Imidazole-1-acetamide, N-(2,3-dihydroxypropyl)-2-nitro- (9CI) (CA INDEX NAME)



L11 ANSWER 60 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1969:422065 CAPLUS
DOCUMENT NUMBER: 71:22065
TITLE: Studies in the nitroimidazole series. III. 2-Nitroimidazole derivatives substituted in the 1-position
AUTHOR(S): Beaman, Alden G.; Tautz, William; Duschinsky, Robert
CORPORATE SOURCE: Chem. Res. Dep., Hoffmann-La Roche, Inc., Nutley, NJ, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1961-70) (1968), Volume Date 1967 520-30
CODEN: AACBAX; ISSN: 0074-9923
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA issue.
AB Derivs. of 2-nitroimidazole (I), which is active against Trichomonas infections, are prepd. Of the prepd. derivs., those with a substituted 2-propanol group in the 1 position exhibited the best activity against Trichomonas vaginalis in mice. These compds. were prepd. by the reaction of I with the appropriate 1,2-epoxy-3-substituted propane in refluxing water, EtOH, or excess propane deriv. in the presence of K2CO3, NaOH, or aq. NH3. II prepd. in this manner were (R, m.p., and % yield given): OH, 110-12.degree., 43; Cl (III), 156-8.degree., 78; MeO (IV) 110-11.degree., 72; PhO, 142.5-3.5.degree., 60; 2,4-Cl2C6H3O, 160-2.degree., 64; PrO, 74.5-6.0.degree., 20; allyloxy (V) 57.5-8.5.degree., 46. Similarly 4,5-dimethyl-2-nitroimidazole with epichlorohydrin and 1,2-epoxy-3-methoxy-2-propanol gave 43% 1-(4,5-dimethyl-2-nitro-1-imidazolyl)-3-chloro-2-propanol, m. 165.5-6.5.degree., and 54% 1-(4,5-dimethyl-2-nitro-1-imidazolyl)-3-methoxy-2-propanol, m. 120-1.degree., resp. Other active compds. against Trichomonas infections were amide derivs. of 2-nitroimidazole-1-alkanoic acids. Some of these amides were prepd. by the reaction of the Na salt of I with an alkyl .omega.-haloalkanoate in HCONMe2 at 100-150.degree. followed by reaction with an amine in MeOH at 25.degree.. VI prepd. by this method were (n, R, R1, m.p. and % yield given): 1, H, Bu, 124-5.degree., 82; 1, H, MeCH(OH)CH2, 162-3.degree., 75; 1, Me, Me, 129-130.degree., 81; 1, H, 3,4-(MeO)2-C6H3CH2CH2, 150.5-1.0.degree., 89; 1, H, 2-pyridylmethyl, 162.5-3.5.degree., 72; 1, H, 4-amino-2-methylpyrimidin-5-ylmethyl, 299-300.degree. (decompn.), 58; 3, Me, Me, 88-9.degree., 27. Similarly prepd. were: 62% N-iso-Pr, m. 153-4.degree., and 83% N-benzyl, m. 151.0-1.5.degree., derivs. of 2-hydroxy-3-(2-nitroimidazol-1-yl)propanamide. Several other amides are prepd. by a more general method

L11 ANSWER 60 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
in which an N-substituted or N,N-disubstituted .omega.-haloalkanoic acid amide is prepd. in H2O at 0.degree. from an .omega.-haloalkanoic acid chloride and an amine and is treated with the Na salt of I in HCONMe2 at 100-150.degree.. VI (n = 1, R1 = H) prepd. by this method were (R, m.p. and % yield given): H, 182.0-3.5.degree., 69; Me, 174-5.degree., 87; p-MeOC6H4, 207.0-7.5.degree., 66; o-O2NC6H4CH2-, (2 forms m. 166.5-8.5.degree. and 175.5-6.5.degree.), 68. Lower activity and usually higher toxicity were exhibited by 1-(substituted benzyl) derivs. of I prepd. from the Na salt of I and a benzyl halide. These compds. were: 83% 1-(p-nitrobenzyl)-2-nitroimidazole, m. 130.0-1.5.degree., and 46% 1-(p-chlorobenzyl)-2-nitroimidazole, m. 108.0-9.5.degree.. The following preps. of various derivs. of the above compds. are also described.
III was treated with NaOH to prep. 89% 1-(2,3-epoxypropyl)-2-nitroimidazole, m. 53.5-5.0.degree.. IV treated with CrO3 gave 67% 1-(2-nitro-1-imidazolyl)-3-methoxy-2-propanone, m. 65-6.degree.; semicarbazone m. 181-3.degree.. III was also converted to its anisate (m. 73-5.degree., 69% yield) and its acetate (m. 62-4.degree., 41% yield) by the usual methods. IV was treated with Br to give 1-(2-nitro-1-imidazolyl)-3-(2,3-dibromopropoxy)-2-propanol, m. 71-3.degree.. I treated with NaOMe and ClCH2CO2Me or Cl(CH2)3CO2Me gave 91% Me (2-nitro-1-imidazolyl)acetate, m. 94-5.degree., and the corresponding butyrate. N-(o-Nitrobenzyl)chloroacetamide (m. 92.5-4.5.degree., 30% yield) was prepd. from o-nitrobenzylamine-HCl and ClCH2COCl. A mixt. of I, K2CO3, EtOH, and Et glycidate was refluxed to prep. 87% Et 3-(2-nitro-1-imidazolyl)lactate, m. 147.0-8.5.degree.. N-Methyl-(4,5-dimethyl-2-nitro-1-imidazolyl)acetamide (m. 170-2.degree., 27% yield) was prepd. by treatment of 4,5-dimethyl-2-nitroimidazole with NaOMe and ClCH2CONHMe.
IT 22668-00-4P
RL: SPN (Synthetic preparation); PREP (Preparation) (prepn. of)
RN 22668-00-4 CAPLUS
CN 1H-Imidazole-1-acetamide, N-butyl-2-nitro- (9CI) (CA INDEX NAME)



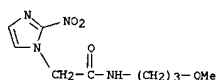
L11 ANSWER 60 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)

L11 ANSWER 61 OF 62 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1969:403383 CAPLUS
DOCUMENT NUMBER: 71:3383
TITLE: Biocidal (2-nitroimidazolyl) alkanolic acids and derivatives
PATENT ASSIGNEE(S): Hoffmann-La Roche, F., und Co., A.-G.
SOURCE: Brit., 20 pp. CODEN: BRXXAA
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:
PATENT NO. KIND DATE APPLICATION NO. DATE
GB 1138529 19690101
PRIORITY APPLN. INFO.: US 19660418
AB The title compds. are prepd. Thus, to a slurry of 100 g. powd. sublimed 2-nitroimidazole (I) in 500 ml. HCONMe2 is added 200 ml. 4.44N NaOMe in MeOH, followed by just sufficient I to change the color of the soln. from pink to yellow, the soln. heated at 153.degree. to remove MeOH, cooled to 90.degree., 135 ml. ClCH2CO2Me added (the temp. first rising spontaneously to 122.degree. and then falling), the mixt. heated 15 min. at 105-115.degree. and worked up to give 12 g. Me ester (II) of (2-nitroimidazolyl)acetic acid (III), pale yellow, m. 94-5.degree. (EtOH). Similarly prepd. are the Et ester of 3-(2-nitroimidazolyl)propionic acid (IV), m. 47.5-49.degree. (CCl4), methyl 4-(2-nitroimidazolyl)butyrate and methyl 5-(2-nitroimidazolyl)valerate. A soln. of 20 g. II in 1200 ml. 0.1N NaOH is refluxed 15 min., cooled, acidified (pH 1.7) with 120 ml. HCl, and extd. with 3 .times. 100 ml. EtOAc to give III, m. 159-60.degree. (explodes; decompn. point depends on heating rate). HOCH2CH2NH2 (10 ml.) is added to a stirred slurry of 10 g. II in 50 ml. abs. EtOH the mixt. kept 18 hrs. at room temp. (solid began forming after 15 min.), cooled 7 hrs. in the freezer, the solid filtered off, washed with 2 .times. 10 ml. abs. MeOH, and dried to give III 2-hydroxyethylamide, m. 162-3.degree. (abs. EtOH). Similarly prepd. are the following amides of III (R in CONHR and m.p. given): PhCH2, 188.5-90.degree.; MeO(CH2)3, 118-19.degree. (EtOAc); furfuryl, 179-80.degree.; NHR = morpholino, 113.5-15.degree.; NHR = piperidino, 102-3.5.degree. (EtOAc); 2-ClC6H4CH2, 208-9.degree.; 3-pyridyl, 194-5.5.degree.; 2-pyridyl, 162.5-3.5.degree. (H2O); H2NCH2CH2, 189-90.degree. (decompn.); 3,4-(MeO)2C6H3CH2CH2, 150.5-1.degree.,

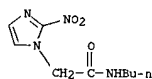
L11 ANSWER 61 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 2-ONC6H4CH2 (V), 175.5-6.5.degree.; 4-MeOC6H4CH2, 211-11.5.degree.;
 5-(2-methyl-4-aminopyrimidinyl)methyl, 299-300.degree. (decompn.)
 (H2O); 2-imidazolyl, 241-2.degree. (decompn.) (H2O); 4-H2NC6H4-CH2,
 208-9.degree.. Also prepd. are R(CH2)nCONR1R2 (VI) (R is
 2-nitroimidazolyl) (n, R1, R2, and m.p. given: 3, Me, H,
 125-6.degree.; 3, Me, Me (VII), 88-9.degree.; 3, Me2CHCH2, H, 79.5-81.5.degree.; 4,
 Me, H, 94.5-6.5.degree. (25:2 benzene-EtOH); 4, Me, Me, 85.5-7.degree.
 (CCl4). A soln. of 3.11 g. I in 30 ml. HCONMe2 and 6.09 ml. 4.52N NaOMe in
 MeOH is heated to 152.degree., cooled to 110.degree., 6.35 g.
 ClCH2CONHC6H4NO2-2 added, the mixt. heated 30 min. at 100-120.degree., concd. at
 60.degree. in vacuo, the residual oil dissolved in 25 ml. abs. EtOH, and kept
 over the weekend to give V, m. 166.5-8.5.degree. (EtOH); similarly prepd.
 is III 4-aniside, m. 207-7.5.degree. (EtOH). A soln. of 13.4 g. NaOH
 in 120 ml. distd. H2O is cooled to 0.degree., 24.1 g. Me2CHNH2 added,
 the soln. cooled to 0.degree., 26 g. Cl(CH2)2COCl added dropwise with
 vigorous stirring at 0-8.degree., and the mixt. stirred a further 10 min. to
 give Cl(CH2)2CONHOMe2 (VIII), m. 69-70.5.degree. (H2O). Similarly prepd.
 are the following X(CH2)nCONR1R2 (X, n, R1, and R2 given): Cl, 3, Me, Me,
 (oil); Cl, 3, Me2CH, H (m. 52-4.degree.); Cl, 3, Ph-CH2, H (m.
 66-7.5.degree.); Cl, 4, Me2CH, H (oil); Br, 5, Me2CH, H (solid); Br,
 5, Me, H (oil); Br, 5, Me, Me (oil); Br, 5, PhCH2, H [m. 55-7.degree.
 (Et2O)]. I (2.22 g.) is dissolved in 4.3 ml. 4.56N NaOMe in MeOH, a
 pinch of I added to change the color of soln. from orange to yellow, 20 ml.
 HCONMe2 are added, the soln. heated to 152.degree., cooled to
 110.degree., 3.12 g. VIII added, the mixt. stirred 4 hrs. at 110-130.degree., and
 worked up to give IV isopropylamide, m. 117-18.degree. (abs. EtOH).
 Similarly prepd. are VI (n, R1, R2, and m.p. given): 3, Me2CH, H,
 103-3.5.degree.; 3, PhCH2, H, 89.5-90.degree.; 4, Me2CH, H,
 83-3.5.degree. (CHCl3-CCl4); 5, Me2CH, H, 87-8.degree. (distd. H2O); 5, Me, H,
 95-7.degree.; 5, Me, Me, 73.5-5.5.degree.; 5, PhCH2, H,
 103-4.5.degree.; and VII, m. 86-7.5.degree.. A mixt. of 10 g. powd. and sieved
 sublimed I, 1 g. anhyd. K2CO3, 100 ml. abs. EtOH and 20.78 g. Et glycidate (d.
 1.093, b. 77-9.degree./34 mm.) is refluxed with stirring until the uv
 spectrum in 0.1N base had a max. at 327 m.mu., and no shoulder at 375 m.mu.
 (.apprx.40

L11 ANSWER 62 OF 62 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1969:10175 CAPLUS
 DOCUMENT NUMBER: 70:10175
 TITLE: Antiprotozoan and antibacterial activity of
 2-nitroimidazole derivatives
 AUTHOR(S): Grunberg, Emanuel; Beskid, G.; Cleeland, R.;
 DeLorenzo, W. F.; Titzworth, E.; Scholer, H. J.;
 Richle, R.; Brenner, Z.
 CORPORATE SOURCE: Dep. of Chemother., Hoffmann-La Roche, Inc.,
 Nutley, NJ, USA
 SOURCE: Antimicrobial Agents and Chemotherapy (1961-70)
 (1968), Volume Date 1967 513-19
 CODEN: AACHA; ISSN: 0074-9923
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Three propanols [1-(2-nitro-1-imidazolyl)-3-methoxy-2-propanol (I);
 3-(2-nitro-1-imidazolyl)-1,2-propanediol (II);
 1-(2-nitro-1-imidazolyl)-3-allyloxy-2-propanol (III)], 4 amides
 [N-butyl-2-nitro-1-imidazoleacetamide (IV); N-(2-hydroxyethyl)-2-nitro-1-imidazoleacetamide (V);
 N,N-dimethyl-2-nitro-1-imidazolebutyramide (VI);
 N,N-dimethyl-2-nitro-1-imidazoleacetamide (VII)], and one benzyl deriv. [1-p-nitrobenzyl-2-
 nitroimidazole (VIII)] all exhibited low-to-moderate degrees to acute
 toxicity in mice. All but V, as judged by the 50% curative dose,
 showed moderate-to-marked activity against Trichomonas vaginalis and
 Trichomonas fetus infections in mice when administered orally, and against the
 local T. vaginalis infection when given s.c. I and VIII were moderately
 active against Entamoeba histolytica in the intracecal infection of rats.
 I was also effective both orally and s.c. against a hepatic infection of
 hamsters due to E. histolytica. All were inactive against
 Trypanosoma brucei and Trypanosoma equiperdum infections in mice. I, III, and
 VIII exhibited a slight effect against Trypanosoma cruzi, i.e., a delay of
 4-7 days in the emergence of trypanosomes in treated animals, as
 compared to untreated controls. II was highly active both prophylactically and
 therapeutically against T. cruzi. None showed activity, either
 orally or s.c. against lethal systemic infections of mice due to Pseudomonas
 aeruginosa or Proteus vulgaris. V and VIII exhibited at
 slight-to-moderate effect against Streptococcus pyogenes, while
 slight-to-marked activity against Escherichia coli was noted with
 III, V, VI, and VIII when the drugs were given orally or s.c. The most
 consistent antibacterial activity observed was against Staphylococcus aureus;
 I, II,

L11 ANSWER 61 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 mins.), filtered and the filtrate refrigerated .apprx.2 hrs. to give
 the Et ester (IX) of 3-(2-nitroimidazolyl)lactic acid (X), m.
 147-8.5.degree. (EtOH). IX (1.4 g.) is added to a stirred soln. of 5 ml. PhCH2NH2 in
 27 ml. abs. MeOH, the soln. stirred overnight at room temp., allowed to
 evap. gave X benzylamide, m. 151-1.5.degree. (EtOH). Similarly prepd. are
 amides of X. (R in COHR and m.p. given): 3-MeO(CH2)3, 111-12.degree.,
 (NHR)piperidino, 131-2.degree.; Me2CHCH2, 136-7.degree., Me,
 129-32.degree.; Me2CH, 152.5-3.degree., (NHR =)NMe2, 130-1.5.degree..
 A soln. of 2.39 g. 4,5-dimethyl-2-nitroimidazole in 4 ml. 4.44N
 methanolic NaOMe is evapd. in vacuo, the residual solid and 2.38 g. ClCH2CONHMe
 dissolved in 25 ml. HCONMe2, refluxed 15 min., the solvent removed in
 vacuo and the residue worked up to give N-methyl-2-(4,5-dimethyl-2-
 nitroimidazolyl)-acetamide, m. 170-2.degree. (CHCl3). The title
 compds. are active against bacteria, pathogenic yeasts, and are
 useful in treating diseases caused by Trichomonas vaginalis, T.
 foetus, Histomonas meleagridis, Trypanosoma cruzi, Trypanosoma rhodesiense,
 and Trypanosoma congolense. 5 examples of pharmaceutical formulations are
 provided.
 IT 22813-34-9P
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. of)
 RN 22813-34-9 CAPLUS
 CN Imidazole-1-acetamide, N-(3-methoxypropyl)-2-nitro- (8CI) (CA INDEX
 NAME)



L11 ANSWER 62 OF 62 CAPLUS COPYRIGHT 2003 ACS (Continued)
 III, V, VI and VII showed activity ranging from slight to marked when
 administered orally, s.c., or by both routes.
 IT 22668-00-4
 RL: BAC (Biological activity or effector, except adverse); BSU
 (Biological study, unclassified); BIOL (Biological study)
 (bactericidal activity of)
 RN 22668-00-4 CAPLUS
 CN 1H-Imidazole-1-acetamide, N-butyl-2-nitro- (9CI) (CA INDEX NAME)



=> fil stnguide

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
281.65	884.52

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
-40.36	-40.36

CA SUBSCRIBER PRICE

FILE 'STNGUIDE' ENTERED AT 16:11:00 ON 12 FEB 2003
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Feb 7, 2003 (20030207/UP).

=>

---Logging off of STN---

=>

Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
0.42	884.94

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
0.00	-40.36

CA SUBSCRIBER PRICE

STN INTERNATIONAL LOGOFF AT 16:15:14 ON 12 FEB 2003